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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

AUGUST, 1931

ORIGINAL ARTICLES.

PRESENT STATUS OF THE CLASSIFICATION, PATHOLOGY AND ETIOLOGY OF CHRONIC RHEUMATIC DISEASE.

JOSEPH L. MILLER, M.D.,

CHICAGO, ILL.

ONE of the outstanding problems in chronic arthritis is uniformity of classification. Much of the literature on this subject is unintelligible on account of the failure to specify the particular type of disease under discussion. Very frequently no attempt is made to differentiate the two types. Even when such a distinction is made, the terms may be confusing.

Classification.—Both from a pathologic and clinical standpoint, two fairly easily distinguishable types can be recognized. These two types are probably etiologically different and not unlikely require different therapy. At the recent congress at Liége it was decided that at least for statistical purposes a uniform nomenclature should be adopted for English, German and French writers. In English the two terms recommended were rheumatoid arthritis (infective periarthritis) and osteoarthritis. Some of the terms which in the past have been used synonymously with rheumatoid arthritis are: atrophic arthritis, chronic infective arthritis and arthritis deformans. Hypertrophic arthritis is synonymous with osteoarthritis. The pathologic studies of Nichols and Richardson[1] led them to use the pathologic descriptive term, "proliferative arthritis," corresponding to the clinical rheumatoid arthritis, and "degenerative arthritis," corresponding to the clinical osteoarthritis. Their studies gave us for the first time a clear pathologic picture of the two types.

The not infrequent presence of mixed forms, that is, rheumatoid arthritis and osteoarthritis, in the same patient has given rise to considerable confusion. In this presentation an attempt will be made to clarify this point. If we include mixed forms in our classification at least 95 per cent of cases can be properly assigned.

Pathology of Rheumatoid Arthritis.—The outstanding contribution to the literature on joint pathology in chronic arthritis is the work of Nichols and Richardson. Recently their findings have largely been confirmed, with some additions, by Fisher.[2] From the standpoint of etiology they both emphasize the importance of studying the changes that occur very early in the disease, as the later changes may be due, in part, to trauma or unequal pressure on the joint cartilages following the initial lesion. The following description of pathologic changes is derived largely from these two sources.

In the earliest stage there is a round-cell proliferation, beginning at the junction of the synovium with the articular cartilage. This cellular proliferation slowly spreads over the articular surface until the entire cartilage is covered by a highly vascular membrane resembling granulation tissue. This pannus invades the superficial layers of cartilage which it destroys. This granulative tissue is later replaced by connective and finally by fibrous tissue. The articular surface eventually is covered with a dense fibrous tissue. The synovial round-cell infiltration is not confined to the articular surfaces, but extends into the periarticular tissues, thus accounting for the spindle-shaped deformity. Fibrosis develops later and may become a contributing factor in ankylosis.

Simultaneous with the synovial changes there is a marked round-cell infiltration and proliferation of the villi. The villous outgrowth may extend to the center of the joint. The vessels in these villi later undergo an obliterative endarteritis, leading to necrosis and fibrosis.

While the above inflammatory reactions are taking place, and sometimes subsequent to them, changes can be observed in the subarticular cancellous spaces. Connective-tissue cells appear in the narrow spaces associated with the development of new blood-vessels and eventually bone absorption, resulting in enlarged cancellous spaces. Later, the subarticular bone shows an increased density. The deep layers of the joint cartilage, adjacent to the head of the bone, are attached from below, undergoing changes similar to those described in the superficial layers. The fibrous covering of the articular surface, therefore, is made up of two superimposed layers—one arising from the hyperplasia of synovium; the other from the subarticular bone.

The above-described lesion does not usually involve all the cartilaginous surface equally; rather there is a tendency to a patchy disintegration. In some areas there may even be an attempt at proliferation of cartilage. In other areas the cartilage may be

destroyed before new fibrous tissue is found, and the bone thus exposed may lead to a bony ankylosis with the adjacent bone on the opposing joint surface. Fibrous ankylosis, however, is much more frequent. In case fibrous ankylosis has taken place, new cartilage and bone may be formed in the fibrous tissue, leading to the second type of ankylosis. By regular movement of the joint throughout the disease, fibrosis and bony ankylosis may be prevented.

There is a secondary bone atrophy, as shown by the Roentgen rays, which at least in part is due to disuse and is most marked in those cases with ankylosis.

The character of the joint changes speaks strongly for an infective origin. This view receives further support by the finding of micro-organisms, in a limited number of patients, in the blood, joint fluid and adjacent lymph glands. Fisher[2] claims that there is no essential difference in the gross or microscopic pathology of the joint in rheumatoid and gonorrheal arthritis.

Pathology of Osteoarthritis.—The changes in the joint, as described by Nichols and Richardson and Fisher, are degenerative, not inflammatory. The earliest lesion found is fibrillation of the cartilage. Normal cartilage on bending shows striæ. Fibrous tissue develops in these striæ, resulting in ridging of the cartilage followed by vertical cracking. These changes are most marked toward the center of the joint. This is possibly due to poor vascularity. Following the cracking, the cartilage degenerates, often giving an irregular pitted appearance. The bottom of the pit may show exposed bone. In addition, the joint surface may show rounded elevations due to proliferation of cartilage, and these areas may later ossify. The new bone formation usually begins long before the cartilage is destroyed.

The peripheral cartilage may remain normal for years after the central portion has degenerated. Sooner or later, however, the marginal cartilage undergoes a hyperplasia, resulting in lipping. Fisher looks upon this as a compensatory reaction to increase the articular surface. Later, this marginal lip undergoes ossification, giving rise to the osteophytes which characterize this type of arthritis. The bone beneath the cartilage increases in density even before the degeneration of the cartilage.

In contradistinction to the rheumatoid type, changes in the synovium develops only after lipping has appeared and is limited to a proliferation of the villi. Existing villi hypertrophy and new villi are formed. Chondromata may develop in the villi and later become detached, and in this manner loose bodies are formed. Their presence may account for the recurrent synovitis so frequently observed in patients with osteoarthritis. The villous proliferations differ from those observed in rheumatoid arthritis, not only in their later appearance, but also in the form of the villi—they are much shorter, do not extend over the entire joint surface and do not show

the same tendency to degeneration. The crunching sound elicited in the knees in osteoarthritis is due to rubbing together of these villous masses.

Bony or fibrous ankylosis in osteoarthritis is practically unknown; interference with motion arises from interlocking of the osteophytes. Muscle atrophy when present is rarely marked, and consequently the deformities observed in rheumatoid arthritis are lacking.

From a pathologic viewpoint it is apparent that chronic arthritis may be divided into two distinct types. Such difference in pathology strongly suggests a difference in etiology.

Etiology of Rheumatoid Arthritis.—There is abundant clinical evidence that rheumatoid arthritis is infective in character. It appears with the most acute onset in children and is frequently referred to as Still's disease. Fever, leukocytosis, inflammation of the joints, enlarged spleen and lymphatic glands is abundant evidence of its infective nature. The disease in adults is usually more insidious in its onset. It appears most frequently in a phalangeal articulation, and there may be only moderate evidence of infection. In the early stages there is always some evidence of inflammation. The course of the disease is usually one of remissions and exacerbations, with a tendency for the evidence of infection to disappear, leaving, however, the characteristic spindle-shaped deformity. In such a joint there may not be any evidence of infection. Not knowing the previous history, one might be led to conclude that the disease was not infectious. This, I believe, explains the position of some orthopedists, that this represents a distinct type to which they apply the term atrophic arthritis. In some cases, not necessarily of long standing, the active disease may entirely disappear, and not infrequently permanently, leaving, however a crippled patient with atrophied and distorted extremities.

The result of blood, lymph gland and joint cultures during the stage of activity lends support to the infective view. Rosenow[3] cultured the regional lymph glands in 54 patients. In 32 he recovered nonhemolytic streptococci. Billings, Coleman and Hibbs,[4] made cultures of regional lymph nodes in 28 patients. Of these 19 showed nonhemolytic streptococci, 1 showed a hemolytic streptococci and 1 a mixture of the two forms. They made joint cultures in 19 patients, 5 of whom showed nonhemolytic streptococci and 1 a mixture of hemolytic and nonhemolytic streptococci.

Richards[5] made blood cultures from 104 patients with "chronic arthritis" and recovered Streptococcus viridans in 18.

Cecil, Nicholls and Stainsby,[6] with care in the selection of cases, obtained positive streptococcus cultures from the blood in 61.5 per cent of patients. Of these streptococci 83.3 per cent he considered attenuated hemolytic streptococci, the remainder being viridans or indifferent strains.

Forkner, Shands and Posten[7] secured positive joint cultures in

22 per cent of their cases. Positive cultures from the neighboring lymph nodes were obtained in 47 per cent. The microörganism in both joint and gland was a nonhemolytic streptococcus.

Cecil, Nicholls and Stainsby[8] have obtained cultures of streptococci from the joints in 33 out of 49 patients or in 67.3 per cent. Cultures obtained from both blood and joints were agglutinated in a very high titer by the patient's blood.

Other investigators, however, have found staphylococci and diphtheroids rather than streptococci. The predominance of streptococci in cultures speaks strongly for this being the most frequent causal agent. However, it speaks against a specific streptococcus as the etiologic agent. Whether rheumatoid arthritis is due to a specific streptococcus, or whether different microörganisms are capable of producing these changes, is still an open question.

Dawson, Olmstead and Boots[9] made agglutination tests with various strains of streptococci, using serum from patients with rheumatoid arthritis. They found that the serum agglutinated all strains of hemolytic streptococci in a very high titer. The agglutinating was just as marked with cultures from erysipelas, scarlet fever or rheumatic sore throat as with the special Streptococcus hemolyticus isolated by Cecil from rheumatoid arthritis.

No attempt will be made to discuss the possible allergic character of rheumatoid arthritis. If it can be demonstrated that a synovial proliferation may be a type of allergic reaction, then allergy must be considered as a possible etiologic factor.

The focus from which the bacteria reach the blood stream and finally the articular surface is so highly speculative that discussion is futile. Some emphasize especially the digestive tract or urinary tract, others the teeth and tonsils and, finally, there are those who believe that acute nasopharyngeal or tracheal infections (rather than chronic foci) are responsible for the joint involvement.

Patients with rheumatoid arthritis show marked evidence of vascular disturbance in the involved extremity. Pale and cold skin is apparently a constant accompaniment of this disease. The beneficial results of ganglionectomy described by Rowntree and Adson[10] suggest that ischemia may be an important factor in preventing recovery. They claim that in the more acute types of rheumatoid arthritis evidence of inflammation readily subsides after the operation. Rowntree believes that ischemia may be an important etiologic factor. This is in accord with Llewellyn's[11] observations, that evidence of inadequate blood supply precedes the joint involvement.

Etiology of Osteoarthritis.—The pathology of the joints, at least of the extremities, that has been studied and the clinical signs and symptoms indicate a noninfective etiology. Many theories have been advanced as to the etiologic agencies that might explain degeneration of cartilage, which is the outstanding pathologic finding.

Fisher claims "osteoarthritis is not a disease *sui generis*, but a physiological response to some form of irritation either mechanical or chemical." He arrived at this conclusion after a careful study of the normal and pathologic physiology of the knee joint. He did some experimental work on rabbits by shaving off a thin layer of cartilage from the center to the periphery of the articular cartilage. Six weeks later the animals were killed. The central portion of this cartilage showed no tendency to regenerate; in fact, it was necrotic. The peripheral portion, however, showed marked regeneration. He concludes that trauma, which will cause degeneration of the central cartilage, is followed by proliferation of the marginal cartilage. This difference in reaction he ascribes to the better vascularity of the peripheral portion. It is his opinion that damage or loss of the central cartilage gives rise to a sequence of events physiologic and compensatory in character which we recognize as osteoarthritis.

Key[12] has discussed the relation of traumatic or mechanical factors to experimental osteoarthritis. In addition to his own experimental work, he reviews the literature on this phase of the subject. The earliest experiments were performed by Axhausen, who destroyed a portion of the knee cartilage in rabbits with iodin or ammonium hydroxid. When the animal was killed after a lapse of several weeks the pathologic changes in the joint resembled those found in osteoarthritis in man. Others have obtained similar results by impairing the blood supply to a portion of the cartilage or by traumatizing the joint. Key has produced osteoarthritis in rabbits by resecting a small piece of cartilage from the patella and at the same time causing unequal pressure or strain by giving the rabbit a knock knee. Pemberton[13] refers to work done by one of his associates. A purse-string ligature was tied around the patella of a dog, which interfered with the blood supply. Later, osteophytes developed on the patella. These few references do not by any means exhaust the literature on this subject, but the results from various sources are in unison.

Key has discussed trauma as an etiologic factor in osteoarthritis in man. He cites instances where acute trauma has been followed by osteoarthritis. Any disturbance of posture that leads to faulty weight bearing or strain may be a factor in the development of osteophytes. He gives as examples deformities of the feet, improper alignment of fractures, unreduced dislocations and various congenital deformities. As illustrations of acute trauma leading to osteoarthritis, he mentions loose bodies or fractures into the joint. For many years Goldthwaite has emphasized posture as an etiologic factor in osteoarthritis.

The Charcot joint is an osteoarthritis. Here hypermobility and absence of the pain sense permit severe traumatisms and result in a very high-grade osteoarthritis. Heiss,[14] made Roentgen ray exam-

inations of 159 Olympic athletes, at Amsterdam. In 23 he found periosteal thickening or osteophytes. In the football player the changes were found principally in the knee, in boxers chiefly in the elbow and wrists and in javelin and discus throwers in the elbow and shoulder. Baseball pitchers often suffer from osteoarthritis of the shoulder. A famous catcher who squats behind the bat and makes a snappy forearm throw to bases has an osteophyte on the upper third of the humerus at the tendinous attachment of a muscle, probably due to strain. The baseball finger is an osteoarthritis of the interphalangeal articulation of the distal phalanx and has the characteristics of a Heberden node.

Chronic arthritis is one of the great problems in countries where national health insurance is compulsory. A study of workers has shown that the man employed at a machine where he must frequently reach upward and pull a lever develops osteophytes in his elbow or shoulder. If he must frequently press a pedal with his foot he acquires osteoarthritis of this extremity. In England it is reported that of the various trades osteoarthritis is the most frequent in the heavy steel workers.

During the past year I have been interested in noting the frequency of Heberden's nodes in women past sixty years. Examinations of the fingers have shown that at least the majority of these individuals show some osteoarthritis. As a rule, the index finger is involved first, possibly because it is used most or more subjected to mild trauma. Where there is marked osteoarthritis of one finger, and where the other fingers are free, a history of acute trauma of the involved finger can usually be elicited. A woman, aged 45 years, showed marked osteoarthritis of the distal joint of the right middle finger, with beginning Heberden's nodes in some of the other fingers. She promptly volunteered the information that the osteoarthritis on this finger followed injury in a cash register. Another patient, a man, aged 60 years, had a high-grade osteoarthritis on one little finger, with beginning Heberden's nodes on other fingers. He related that when 6 years of age his father whipped him, one severe blow striking the distal joint of the little finger. Shortly after this the joint enlarged. Fifty years later, and probably the result of using his fingers (which is equivalent to repeated slight trauma), he developed similar changes on other fingers.

A woman, aged 35 years, for several years played a great deal of golf. At the beginning of the present season she changed her grip so that there was an interlocking of the little fingers. Within 4 months she developed a Heberden node on one little finger. Recently I saw a masseuse who had unusually marked nodes on the thumbs, with only slight changes on the fingers. She ascribed, and probably correctly, the changes on the thumbs to her custom of exerting pressure lateral to the spine.

Osteoarthritis of the knees is quite frequent in women around

50 years. It is sometimes referred to as chronic arthritis of the menopause. This is found, with rare exceptions, only in women who are overweight. In the past 2 years I have observed only 2 instances where this developed in slender women under 40 years. In both cases the trouble followed acute injury to the knee. In both of these patients one knee was injured playing hockey. Grating and pain in the joint appeared a few months after the injury. The other knee was injured in 1 patient by falling on the ice and in the other by being thrown from a horse and dragged with one foot in the stirrup. Key believes that osteoarthritis of the knees is in part due to unusual weight bearing, and in addition obesity tends to pronation of the feet and a slight valgus deformity of the knees, thus adding the factor of strain.

The spine is the point of selection for osteoarthritis. Changes here are rare under 20 years of age unless there is a history of acute trauma, which may be followed by a localized osteoarthritis; or, in case of scoliosis, when osteophytes may develop on the convexity due to unusual pressure or strain. A localized trauma of the spine, producing a fracture of a vertebra, may be followed by the outgrowth of osteophytes not only on the injured vertebra but also on the immediate adjacent vertebræ, which at most were not severely traumatized. The resulting splinting appears to be a purposeful physiologic response.

Schanz[15] reports the presence of a localized osteoarthritis of the spine in aortic aneurysm, with bone erosion.

Past 40 years osteoarthritis of the spine increases with each decade. Allard,[16] in 2000 Roentgen rays of the spine, taken at the Mayo Clinic, chiefly for a study of the urinary tract, found osteoarthritis of the lumbar spine in 67 per cent of men past 50 years and in 40 per cent of women. Men, on account of their occupations, have more opportunity to traumatize the spine. Jones[17] states: "Its trivial manifestations in some predynastic cemeteries are practically universal in adults and its grave ones far from rare."

There is no doubt that the frequency of osteoarthritis increases with years. Someone has said: "Age represents trauma extending over years." It is claimed that the Egyptian hieroglyphic symbol for old age is the figure of a man crippled with chronic arthritis.

Bauer[18] refers to the observation of Beitzkes, a German anatomist, who studied the knee and great toe joint in 200 cadavers. After 50 years of age the cartilage in 100 per cent of cadavers showed degenerative changes similar to those observed in the early stages of osteoarthritis. Weichselbaum, quoted by Bauer, claimed that the changes in osteoarthritis differed only in degree from those present in the ordinary senile individual. Smith-Petersen,[19] in studying the result of trauma on sacroiliac cartilage, comes to the conclusions that the changes are similar to those due to age.

Pathologic studies of osteoarthritis have been confined largely to the joints of the extremities. I was able to find but few references in the literature on the pathology of spinal osteoarthritis. As we are dealing here with fibrous cartilage, it is possible that it may react in a different manner to mechanical or chemical irritation.

Stockman,[20] in an article on ossifying spondylitis, refers to the "poker spine," where there is a bony encasement of the spine, rendering it immobile. These changes, he believes, are the results of chronic infection, leading to ossification of the interspinous ligaments. In this type the intervertebral disks are also ossified, as distinguished from the ordinary osteoarthritis of the spine where the disks are intact. He believes the typhoid spine falls in this group. However, as we will see later, typhoid may affect the spine in a quite different manner.

Plate[21] discusses the early pathology in osteoarthritis of the spine in elderly people. He states that the first change is loss of elasticity in the intervertebral disks, resulting in some thinning. Following this is evidence of bone rarefaction around the periphery of the vertebra and finally the appearance of osteophytes.

Kaufman[22] claims that the fatty degeneration of cartilage observed in osteoarthritis of the extremities is not usually seen in osteoarthritis of the spine. The first change in this disease, he believes, is impairment of elasticity in the intervertebral disks. It has been claimed that the lessened resiliency of the cartilage by increasing shock is a factor in the development of osteophytes. In elderly persons with spinal osteoarthritis the Roentgen ray occasionally shows thinning of the disks almost to the point of disappearance.

Jones,[23] in his study of ancient Nubian skeletons, has given an excellent description of the gross pathologic changes in this disease. His observations were based on a study of 6000 skeletons. He believes the very earliest change is a thickening of the periosteum at the attachment of the "anterior common ligament of the spine." This attachment is toward the upper surface of the vertebra. A small bony plate appears at this point, which is the beginning of an osteophyte. As this grows upward and touches the lower border of the adjacent vertebra, "as if in response to this new outgrowth of bone, there develops upon either side of the area of contact a bony outgrowth which fuses with the osteophyte from the vertebra below." He refers to the frequency with which the disease remains confined to one side of the body of the vertebra, and such a unilateral development may be present over great lengths of the spinal column without any signs of involvement on the other side. He further relates that the cartilage is little or not at all involved. The first appearance of the osteophyte at a ligamentous attachment suggests strain as an etiologic factor. The limitation of these osteophytes in some cases to only one-half of several consecutive vertebræ also suggests postural strain.

The evidence up to this point strongly suggests mechanical irritation as an important etiologic factor in osteoarthritis. We are not justified, however, in concluding that overuse is in all cases the sole cause.

In 1913 Frederich Muller, at a medical meeting in London, where chronic arthritis was under discussion, emphasized the noninflammatory character of osteoarthritis, and suggested changing the name to "osteoarthrosis." Assmann,[24] who reports the above statement, has recently said that the term "osteoarthritis" is a misnomer and that "osteoarthrosis" or "osteoarthropathy" would be a much better term.

Osteomyelitis is recognized as a complication of typhoid fever. It involves most frequently the ribs and long bones, but occasionally the spine when it may lead to the development of an osteoarthritis.

Rugh[25] reported the autopsy findings in a patient dying from uremia following typhoid fever. The intervertebral cartilage between the third and fourth lumbar vertebræ was destroyed and replaced by fibrous tissue which had in part become ossified. No reference is made to the presence of osteophytes. These findings are similar to those found in rheumatoid arthritis in the extremities.

Gallus[26] made a study of the typhoid spine. He states that the earliest change in the vertebra is a circumscribed bone rarefaction due to infection, followed by the development of osteophytes, and later by destruction of the cartilaginous disks. He claims that the bone may be restored and the osteophytes disappear.

The question arises as to the relation of the infection to the development of osteophytes. Attention has already been called to the appearance of localized osteoarthritis of the spine after severe injury as, for instance, fracture of a vertebra, a change in which infection probably does not play a rôle. It seems quite probable that a vertebra damaged by infection might respond in the same manner as after injury by direct trauma. In each condition the development of osteophytes might be looked upon as a physiologic protective reaction. If this be true, the osteoarthritis is only indirectly due to the infection.

Hollis E. Potter recently showed me a roentgenogram of a typhoid spine. Eight months after recovery from typhoid the patient developed severe localized lumbar pain. The Roentgen ray showed slight rarefaction of a single lumbar vertebra and the presence of an osteophyte. Another osteophyte had grown upward from the adjacent vertebra below. The body of this vertebra was apparently not invaded by the infection. This response is similar to that observed from severe trauma to a vertebra, and might be considered protective in character. Ten months later the patient developed similar changes in a second lumbar vertebra. Localized changes of the same character may occur in osteomyelitis of a

vertebra, due to the staphylococcus, streptococcus or tubercle bacillus, where the damage to the vertebra is much more apparent than in typhoid infection.

Further study is needed to determine whether the infection has actually involved the adjacent vertebræ. If it can be shown that they are not involved, it would be strong presumptive evidence that the outgrowth of the osteophyte was a physiologic response or purposeful reaction, rather than directly due to the infection.

It is apparent that the pathologic changes present in osteoarthritis of the spine do not correspond to those observed in osteoarthritis of the knee. Furthermore, there appears to be several types of lesions in osteoarthritis of the spine. By far the most frequent form is the so-called senile type, which shows an increasing incidence with years. It may develop at any age following acute trauma. The only involvement of the cartilage is loss of resiliency. Here trauma is the outstanding etiologic factor.

A second type of change may be seen in osteomyelitis of a vertebra. The cartilage here is usually destroyed. It is yet to be determined whether injury to the vertebra by the infection is responsible for the growth of osteophytes, or whether they arise as a direct response to the infection.

The "poker spine" has a quite different pathology. The spine becomes encased with a bony sheath, which probably arises from ossification of the intervertebral ligament. The cartilage here is destroyed and replaced by bone, giving rise to a perfectly rigid spine. It is thought that these changes are directly due to infection.

In addition to the three forms here described further study may reveal other distinct types.

Inasmuch as pathologic studies of the joint changes in the extremities have been confined chiefly to the knee, it would be interesting to determine whether the changes in the terminal phalanges, preceding the development of a Heberden node, is of the same character. This might offer insurmountable difficulties. At least, however, the character of the cartilaginous changes in Heberden's nodes could be determined.

Nathan[27] injected 16 dogs intravenously with a culture of hemolytic streptococci. Six animals when killed after 8 to 90 days showed pathologic changes in the spine. In only 1 animal was it limited to the spine; the others had involvement of the joints of the extremities. On opening the spinal canal, focal areas of epidural edema were observed. The epidural periosteum was raised from the underlying bone by this edema. These changes extended into the intervertebral notches. In some areas this edematous area disappeared by absorption; in others it became organized into fibrous nodules. In 1 animal killed after 90 days two connective-tissue nodules were found near the vertebral notches of the fifth and seventh dorsal vertebræ. Such nodules, he believes, might be a

factor in causing root pain. Although no cultures were made from these edematous, other workers have found that they were sterile. If this be true, the changes were probably due to bacterial toxins rather than direct invasion. These experiments should be repeated, allowing the animal to live for a longer time, to note whether these areas become calcified.

The spur on the os calcis, wrongly considered by some as always of gonorrheal origin, nevertheless in some instances bears a direct relationship to this disease. Barr[28] recovered gonococci from the spur in 2 out of 5 cases. Other investigators have failed to substantiate this finding. The location of the spur at a spot where there is pressure and, in addition, traction from the plantar fascia suggests that these factors had something to do with the selection of the site for this particular gonorrheal manifestation.

Wade[29] has recently written a good review of this subject. He calls attention to its frequency in people with flat foot, and considers trauma from tension of the plantar fascia as an important etiologic factor. In a study of 100 cases of os calcis spur at the Mayo Clinic it was thought that occupation played a rôle, as it was more frequent in people who work standing, as, for example, barbers, dentists, motormen and store clerks.

The literature contains very few references to blood and joint cultures in osteoarthritis. Cecil was unable to obtain positive blood cultures in 18 patients with this type of arthritis.

Keys[30] made joint cultures from 39 patients with rheumatoid arthritis and 6 with osteoarthritis. He reported positive cultures in approximately 50 per cent of each group. He found the same microörganisms in both types. The predominating germs were a staphylococcus and a minute bacillus. These were at times found in pure cultures and at other times mixed. In 2 of the mixed cultures he found, in addition, a short-chain, nonhemolytic streptococcus. The finding of staphylococci in rheumatoid arthritis is so at variance with the experience of others that one is led to suspect contamination.

Osteoarthritis is very common in horses over 4 years of age. Webster[31] made cultures from the knees in a considerable number of horses, but with negative results. Hare[32] examined 146 horses about to be slaughtered and found evidence of osteoarthritis in 21. These horses varied in age from 6 to 28 years. After death he made cultures from the synovial fluid and synovial membrane. In 9 animals cultures were positive, but he obtained such a variety of microörganisms that he came to the conclusion that the growths were contaminative.

Mixed Type of Chronic Arthritis.—The presence of both rheumatoid and osteoarthritis in the same individual has been a stumbling block for everyone who has attempted to classify chronic arthritis.

We may be able to explain at least many of these mixed forms

if we accept acute trauma, long-continued mild trauma, age and strain as etiologic factors in osteoarthritis. The presence of osteoarthritis in combination with the rheumatoid type does not mean that the development of osteophytes is directly due to the rheumatoid arthritis; in other words, directly due to infection. The etiologic factor may be strain or pressure consequent to the deformity arising from muscle atrophy. A deformity of the foot due to rheumatoid arthritis might result in strain on the knee, hip or spine, with resulting osteoarthritis. I recently saw a girl, aged 17 years, greatly crippled from a rheumatoid arthritis which first appeared in early childhood. She could only move about in a crouching posture. She had a marked osteoarthritis of the spine, a condition exceedingly rare at this age except as a result of rather marked trauma.

A rheumatoid arthritis of the fingers, with deformity from muscle atrophy, may by causing unequal pressure on the rheumatoid joint lead to the formation of osteophytes.

The individual past 50 years who develops a rheumatoid arthritis probably has already an osteoarthritis of the spine and possibly Heberden's nodes. I have seen several cases of this sort. A patient at any age who develops a rheumatoid arthritis may have previously had a localized osteoarthritis from acute trauma. The pathology of the two types of arthritis speaks very strongly against a common etiology.

Conclusions. Chronic rheumatic joint disease—pathologically, etiologically and clinically—may be divided into two types.

Pathologically, the joint changes in rheumatoid arthritis are inflammatory; in osteoarthritis degenerative.

Etiologically, rheumatoid arthritis is usually and probably always due to an infection. Etiologically, trauma, in the broad sense of the word, is the chief, if not the sole, factor in osteoarthritis of the extremities. It is probably the most frequent factor in osteoarthritis of the spine. Here, however, the pathologic changes are quite different from those observed in the extremities and the possible rôle of infection in certain types cannot be ruled out. For the noninfective type "osteoarthrosis" is a more fitting term than "osteoarthritis."

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THE SIGNIFICANCE OF THE GASTRIC SECRETIONS IN PERNICIOUS ANEMIA.

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The significance of achylia gastrica in pernicious anemia has long been under dispute. The recent work of Castle, however, has indicated that the gastric disorder may be the primary factor in the production of the disease. He demonstrated that typical remissions, similar to those produced by liver, could be induced by the daily administration of 200 gm. of raw beef, previously digested in normal gastric juice, either in the stomach[1] or *in vitro*.[2] Neither the beef nor the gastric juice was effective alone, nor were the two when fed separately. From these experiments, Castle suggested that pernicious anemia is a deficiency disease of a new type, caused by lack of an unknown substance produced from protein during the course of normal digestion, the production of which, however, fails to take place in the deficient gastric juice of pernicious anemia. He, therefore, regards the achylia gastrica as the essential pathologic process. This theory explains remissions following the eating of

liver or kidney by assuming the presence in liver and kidney of the preformed effective substance which does not have to be set free by digestion.

There are several difficulties in the way of a complete acceptance of Castle's theory. First, it fails to explain the spontaneous remissions so characteristic of the untreated disease, during which, as far as we know, there is no change in the character or composition of the gastric juice. Second, it is known that complete gastric achylia may persist for years in apparently healthy people, without the development of any of the evidences of pernicious anemia. Finally, it does not account for the occasional rare patients with blood pictures identical with those of pernicious anemia, who respond typically to liver therapy, but whose gastric juice appears to be entirely normal. That gastric juice which is apparently normal should entirely lack some unknown factor necessary for the activation of the effective substance in beefsteak seems *a priori* to be unlikely, but Castle has recently shown this to be the case. He found that gastric juice obtained from 2 patients with "pernicious anemia" was normal as to its content of acid, pepsin and rennin, but failed, after incubation with beefsteak in the usual way, to produce the substance effective in causing remissions in other cases of pernicious anemia.[3] He assumed, therefore, the presence in normal gastric juice of some unknown factor which did not seem to be present in the juice from his pernicious anemia patients, even though the secretions of the latter seemed normal in every other way.

A finding as striking as this obviously requires confirmation. An opportunity recently presented itself when there were available simultaneously 2 patients, 1 with pernicious anemia and 1 with sprue, both of whom had apparently normal gastric juice and both of whom had responded typically to liver therapy. At the same time there was available a fresh case of typical pernicious anemia upon which the digested material could be tested. As will be pointed out, our observations failed to confirm those of Castle.

Experimental Observations. The experiment consisted, as pointed out above, of the feeding to a patient with typical Addisonian pernicious anemia, of beefsteak, previously digested in the gastric juice of other patients with the blood picture resembling that of pernicious anemia, who had previously responded to liver in the usual way but whose gastric secretion appeared entirely normal. The gastric juice was obtained from 2 patients:

Case 1.—J. G. was a case of sprue who had responded to liver, whose record was previously reported by Bloomfield and Wyckoff.[4] His gastric juice was used only for the first two doses.

Juice for the rest of the experiment was obtained from the other patient, suffering from pernicious anemia, whose clinical record is here included to make clear the nature of her case.

Case 2.—C. M., aged 43 years, a Central American housewife, entered the hospital on May 9, 1925, complaining of indigestion and occasional

diarrhea. Her family history and past history were unimportant. For 10 years she had been troubled with acid eructations, gas and occasional epigastric pain after meals. She was ordinarily constipated but had frequent attacks of mild diarrhea lasting two or three days. Her appetite had been poor for 1 year and she had been weak and tired for 3 months. Her mouth was sore and her ankles became slightly swollen at times.

On examination she was fairly well nourished and did not appear ill. The tongue was pale and smooth. The posterior cervical glands were slightly enlarged. The heart and lungs were negative. The liver and spleen were both palpable just beneath the costal margin. The extremities were negative. The blood count was: Red blood cells, 1,810,000; hemoglobin, 54 per cent (Sahli); color index, 1.75; white blood cells, 5450; polymorphonuclears, 75 per cent; lymphocytes, 24 per cent. The smear showed moderate poikilocytosis, marked anisocytosis, polychromasia, Howell-Jolly bodies and a few normoblasts. An Ewald test meal gave a total acid of 48 degrees and a free hydrochloric acid of 40 degrees, 90 minutes after the meal.

She was discharged, without a definite diagnosis, on Fowler's solution and iron cacodylate. This treatment was continued for two months in the Outpatient Department. She improved subjectively, and the red blood cells increased to 2,890,000 and the hemoglobin to 65 per cent. No cause of the anemia was found on very careful study.

She did not return until she again entered the hospital on April 15, 1930, complaining of indigestion. Her condition during the interval had remained much the same. Her gas, eructations and epigastric pain persisted. She felt quite well at times and at other times was weak and tired. For the last year she had been quite weak and had lost 30 pounds in weight.

The physical examination was unchanged except that the liver and spleen were not felt. Vibratory sensation was normal. The blood count was: Red blood cells, 2,200,000; hemoglobin, 58 per cent (Sahli); color index, 1.3; white blood cells, 6400. The smear showed anisocytosis, poikilocytosis, polychromasia and normoblasts. The icterus index was 11.2 and the indirect van den Bergh 2 units. Gastric analysis after histamin gave:

		histamin ↓			
Time	Fasting	10′	20′	30′	40′
Total acid	5°	10°	20°	68°	84°
Free hydrochloric acid	0	0	7°	58°	72°
Volume in cc.	26	20	22	60	52

A diagnosis of atypical primary anemia was made, and she was placed on ventriculin, 2 vials daily. There was no change in her blood after 10 days, and liver extract (Lilly 343) was substituted for ventriculin in doses of 3 vials daily for 2 days and then 6 vials daily for 16 days. The reticulocytes increased to 9.5 per cent on the tenth day of liver therapy and the hemoglobin rose to about 80 per cent. The red blood count rose to about 3,000,000 after 40 days, as shown in Chart I. She continued to take liver at home and on July 17, 3 months after treatment was started, the red cell count was 4,000,000 and the hemoglobin 76 per cent. She was clinically much improved.

This response was characteristic of that obtained in pernicious anemia. Because of the high initial level of the red cells, a high reticulocyte count or a rapid improvement in the blood could not be expected, as was shown by Minot.[5]

Method. The method used in preparation of the material for feeding was that described by Castle and Townsend.[2] Gastric juice was obtained from Cases 1 and 2 after histamin stimulation, a dose of about 0.7 mg. being given after aspiration of the fasting contents and again after 40 to 60 minutes.

Aspiration was continued until approximately 300 cc. of juice had been secured, and all of it was used each day. The juice contained an abundance of acid. The lowest values in the complete specimens were: Case 1: free hydrochloric acid, 42 degrees; total acid, 70 degrees. Case 2: free hydrochloric acid, 40 degrees; total acid, 55 degrees. The highest value obtained from Case 2: free hydrochloric acid, 90 degrees; total, 110 degrees. The juice was obtained daily and used immediately. It was first filtered through gauze and mixed with 200 gm. of finely ground beef muscle in a large beaker. It was then titrated with concentrated hydrochloric acid to a pH of about 3 (estimated by the production of a distinct red color when a drop of the mixture was added to a small amount of distilled water containing a drop of para-dimethyl-amino-azo-benzol), and placed in an

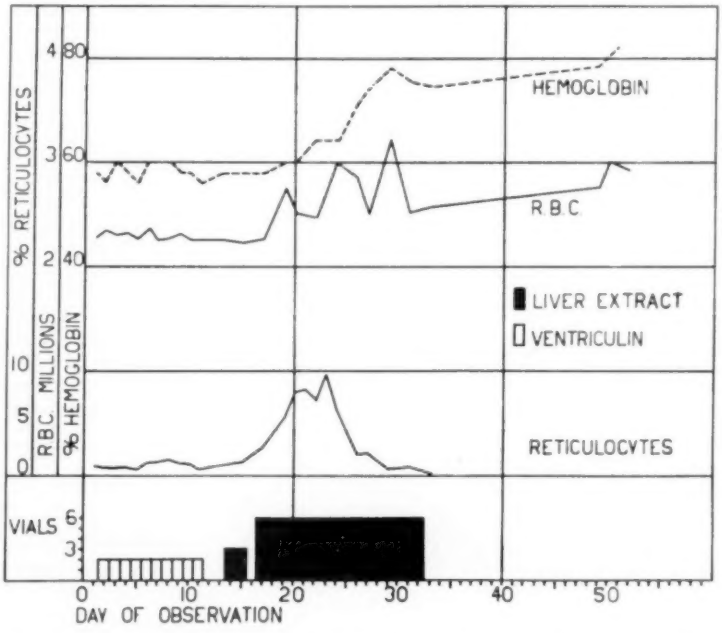

CHART I.—Blood response of a case of "pernicious anemia" with normal gastric juice to ventriculin and liver-extract feeding.

incubator at 37° F. for 2 hours. The mixture was stirred at frequent intervals and the pH maintained by additions of hydrochloric acid when necessary. At the end of the incubation period the mixture was strained through a fine wire sieve and the liquid portion was brought to a pH of about 5 with 5N.NaOH. This was done by titration to about the middle of the range of methyl red. The neutralized material was then introduced, through a stomach tube, into the fasting stomach of Case 3.

Experimental Data. The clinical record of Case 3, used for testing the potency of the digestion mixture, is briefly as follows:

CASE 3.—M. A., aged 55 years, an American housewife, entered the hospital on May 30, 1930, complaining of weakness for 3 years. Her family history and past history were unimportant.

For 3 years she had had intervals of weakness, often with swelling of the

feet, alternating with intervals in which she felt quite well. During this same period she had noted a marked pallor. Her tongue was sore at times. For two years she had had numbness and tingling of her legs, at times severe enough to make walking difficult. She had lost no weight.

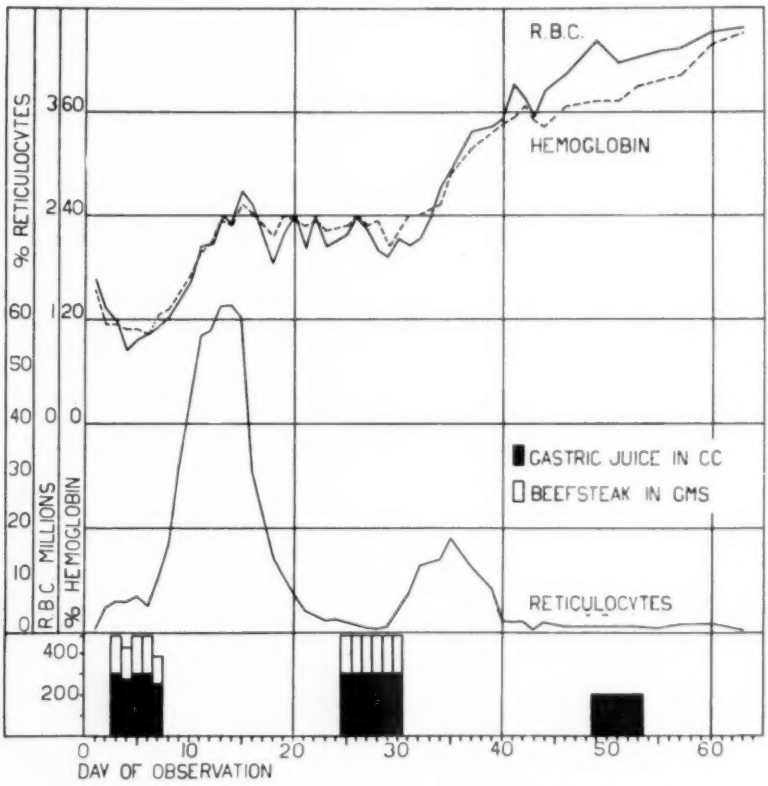

CHART II.—Blood response of a case of pernicious anemia, receiving a mixture of beef and gastric juice from "pernicious anemia" patient reported in Chart I.

On examination she was extremely pale and sallow, but, although rather poorly developed, she was quite well nourished. The tongue showed a practically complete papillary atrophy. The heart was negative and the lungs were normal except for diminished breath sounds at the right base. The spleen was palpable 3 cm. below the costal margin. The reflexes were normal, but joint sensibility was diminished and vibratory sensibility was absent in both legs. There was moderate pitting edema of the ankles. The blood on the third day was: Red blood cells, 700,000; hemoglobin, 18 per cent (Sahli); color index, 1.3; white blood count, 2350; polymorphonuclears, 42 per cent; lymphocytes, 48 per cent; eosinophils, 4 per cent; basophils, 1 per cent; neutrophilic myelocytes, 5 per cent. The reticulocytes made up 6 per cent of the red cells. The smear showed moderate anisocytosis and poikilocytosis, with occasional macrocytes. There were a few cells showing polychromasia and stippling. The icterus index was

13 and the indirect van den Bergh 2 units. Gastric analysis after histamin gave no free hydrochloric acid and the highest 10-minute volume was 4 cc.

This case presented all the cardinal features of pernicious anemia and was an excellent one for determining the potency of the digested beef because of the extremely low red cell count and hemoglobin. The course of her response is shown in Chart II. Because of the severity of her disease, a prolonged control period was considered inadvisable and therapy was started on the third day. According to Minot,[5] the first 4 days of treatment may be safely included in the control period, since this length of time is always required before any response takes place. We have, therefore, a control period of 7 days. During this time the red cells and hemoglobin fell slightly and the reticulocytes remained at about 6 per cent. On the fifth day of therapy the reticulocytes had risen slightly and the sixth day they were 17 per cent, so treatment was stopped. They continued to rise, however, and on the twelfth day reached the extremely high value of 63 per cent. Almost simultaneously with the reticulocyte response the red cell count and the hemoglobin increased, the former by a little over 1,000,000 and the latter by slightly over 20 per cent, where they reached a very definite level. The reticulocytes rapidly fell to below 1 per cent.

Because of the high initial reticulocyte level and the magnitude of the response, the possibility that we were observing a spontaneous remission was considered. To decide this question, the treatment was repeated after the blood had maintained a distinct level for 10 days. This period, together with the first 4 days of therapy, gives a second control period of 14 days. Following the second series of feedings, there was another typical response, the reticulocytes rising to 18 per cent and the red cells and hemoglobin by about the same amounts as observed after the first treatment. During the experiment the patient was, of course, on a diet free from liver and kidney.

During the first series of feedings, due to an oversight, Case 2 was receiving 250 gm. of liver daily, and the first time her juice was used (*i. e.*, for the third dose) she had had this amount 3 hours before aspiration. Since the fasting contents of the stomach were removed and discarded, the actual amount of liver substance transferred to Case 3 must have been extremely small. On each of the 2 subsequent days at least 20 hours elapsed between her liver meal and aspiration. During the second series of feedings she was on a liver-free diet.

Eight days after the reticulocytes had dropped to normal and when the red cell count and hemoglobin had reached an approximate level a series of five daily feedings of 200 cc. of gastric juice from Case 2 was given, without beefsteak, as a control. Following this there was a slight rise in red cells and hemoglobin but no increase in reticulocytes.

Discussion. The character of the response, its time of occurrence and the fact that it could be obtained repeatedly leave no doubt but that in this case the material used was highly potent. The results cited are certainly not in accord with the hypothesis proposed by Castle that pernicious anemia is dependent upon the gastric defect, for the gastric juice of Case 2, typical of pernicious anemia except for gastric secretion, was able to produce from beef muscle a material which caused typical remissions. The results are also opposed to those obtained by Castle, in whose cases, as we pointed out above, the "activating principle" was not demonstrated in otherwise normal juice.

Since the gastric juice of Cases 1 and 2 is able to produce this

antianemic substance, it is, perhaps, remarkable that these patients did not produce remissions in themselves. That they have not merely recovered a normal secretion is demonstrated by the fact that they both require liver to keep their blood in a relatively normal condition. The constituents of their diets while they were anemic are not known, but it is possible that if they had taken large amounts of raw beef they might have had remissions. Another possibility that suggests itself is that only the powerful stimulus of histamin will cause a sufficient secretion of the hypothetical substance which produces an antianemic factor from protein. The treatment of sprue and pernicious anemia with raw beef, accompanied by subcutaneous injections of histamin, would prove or disprove this possibility.

The control experiment in which gastric juice alone was fed is not conclusive. There was a slight increase in red cell count and hemoglobin, but not of the magnitude observed after the digested beef. Moreover, when this therapy was started the blood was still improving slightly. The absence of a reticulocyte response is of no significance because of the high level of the red blood cells at this time and also because a second or third reticulocyte response only follows the administration of a larger dose of the effective substance than the dose that produced the primary response.[5] Wilkinson[6] obtained slight reticulocyte responses from feeding normal gastric juice, but he fed it with meals containing protein, so that the response may well have been due to interaction between the juice and the protein rather than to the juice alone.

We do not believe that the significance of the achylia gastrica in pernicious anemia is as yet entirely clear, and the subject requires much further study. Certainly, in view of the rarity of cases presenting the clinical features of pernicious anemia without the characteristic achylia, the accumulation of a large series of experiments of this sort is a tedious matter, but in view of the contradiction between our results and those of Castle, it is evident that further similar cases must be studied before final conclusions can be drawn.

Summary. 1. The treatment of a patient with pernicious anemia by daily feedings of beef muscle, predigested in the gastric juice of another patient with all the clinical features of this disease except for the achylia gastrica, is reported. An unusually brilliant response resulted.

2. To rule out the chance of a coincident spontaneous remission, the treatment was repeated, after the blood had assumed a constant level, with similar results.

3. Gastric juice alone failed to give a definite response.

4. The bearing of these results on the theory that pernicious anemia is directly dependent on a defect in gastric secretion is discussed.

NOTE.—Since this paper was submitted for publication, on August 29, 1930, another paper by Dr. Castle has appeared in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES for September, 1930. In this paper he anticipates the results just reported and suggests that the explanation might be in a failure of absorption of the effective substance even though properly formed. The adequacy of absorption in our 2 cases has been amply demonstrated, at least as regards liver extract and liver, by their previous therapy, although the possibility of failure to absorb effective substance released from beefsteak has not been excluded.

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POLYPI AND POLYPOID CONDITIONS OF THE GASTROINTESTINAL TRACT.

WITH SPECIAL REFERENCE TO PATHOLOGIC AND RADIOLOGIC ASPECTS.

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A REVIEW of the gradually increasing literature on benign tumors of the stomach and intestinal tract, reported under various titles such as gastric and intestinal polypi, adenomata and polyadenomata of the stomach, gastric and intestinal polyposis, gastritis and colitis polyposa and inflammatory adenomatoid hyperplasia of the gastric and intestinal mucosa, makes it evident that a clearer differentiation of the pathologic condition in a given case and its assignment to its proper group should be made preliminary to a discussion of etiology, incidence, symptomatology, radiologic diagnosis or clinical course.

As many authors have pointed out, the term polypus as used clinically does not connote a homogeneous group and, therefore, has no precise pathologic significance; it is an anatomic or morphologic term applied to a form of growth arising from any of the tissues constituting the walls of the stomach or intestines, or at times from embryonal rests therein. Thus fibromata, hemangiomata, papillomata, adenomata, neurofibromata, lymphangiomata, lipo-

mata, cysts and mixed tissue tumors, have all been found at autopsy or at operation as polypoid growths projecting from the inner or outer coat of the gastrointestinal tract. They may occur either in the stomach or intestine alone or at times in both, and it is important to recognize their similarity in genesis and structure in the two locations. Kaufmann and Hauser observed polypoid involvement of the whole gastrointestinal tract from the cardia to the anus, though the stomach and the large bowel are the situations most frequently involved. When they develop from or beneath the mucous coat, traction during peristalsis apparently is a factor in producing the polypoid form of tumor. They vary in size from growths as small as lentils or peas, in all graduations up to a fetal head; in number they vary from a single growth to as many as 300 or more; they occur at all ages, from childhood onward, but have most frequently been found in persons from 40 to 50 years of age, though presumably their origin was many years earlier. Dieulafoy has remarked that multiple polypi are usually of the same size in a given case, arising as if by simultaneous eruption.

In the stomach they are most frequently found toward the pylorus; they may cover a considerable area or sometimes nearly the whole interior of the organ. Single or multiple polypi may exist for many years without symptoms, and even if symptoms appear they are often due to accidental or mechanical causes or to coincidental disease.

Thus, a number of cases have been reported (Cornil, Chiari, Myer, Cleghorn, Sutherland) in which a gastric polypus has been forced into the pylorus or duodenum, producing partial or complete obstruction, or by traction on the gastric wall has caused intussusception (Chiari, Collier, Wade, Eliason and Wright) of the stomach into the duodenum. Of Balfour and Henderson's 58 cases 10 per cent gave a history of pyloric obstruction, usually intermittent. Cholecystitis associated with gastric polypi has frequently been reported, also pyloric ulcer (Sutherland) and 2 cases of rupture of the duodenum, where a gastric polypus has passed through the pylorus. Cases 2 and 3 reported in this paper gave histories of duodenal ulcer. One of us (Anderson) saw a patient with Dr. G. W. Ross and Dr. A. S. Moorhead, in 1922, a woman, aged 42 years, complaining of severe stabbing pain above and to the right of the navel coming on suddenly after breakfast, lasting for an hour and then disappearing until the following morning. Later the abdominal pain became more continuous and associated with persistent vomiting. At operation a small myxomatous polypus was found projecting from the mucous membrane of the upper part of the jejunum and producing intussusception. Excision of some 5 inches of the involved bowel and end-to-end anastomosis was followed by an uneventful recovery.

As a rule, the symptoms produced by polypi are not continuous

or progressive, as one might anticipate, but rather long periods of quiescence may intervene. The disappearance of symptoms may be due to the subsidence of an associated disease, such as cholecystitis, or to the fact that mechanical symptoms (swelling, volvulus, intussusception, pressure) are not necessarily continuous.

Gastric polyps did not escape the attention of Morgagni, though Cruveilhier has priority (1829) in having recognized more fully the nature of the condition. In his opinion gastric polypi were not rare; they were usually multiple, either sessile or pediculated; originated from the otherwise unaltered mucosa; were found in the intestine as well as in the stomach; in 1 of his cases intussusception and in another pyloric obstruction occurred; they might be present without symptoms; in 1 case cancerous transformation had occurred in one of a group of multiple polypi.

Andral differentiated them from cancerous growths. Rokitansky, in his experience of over 30,000 autopsies, observed cases of gastric polypus, and states the mucous membrane may sometimes be warty and rugged from the increase in size of their papillæ and follicles, and that various duplications and prolongations may occur consisting of two varieties of permanent inequality—the mucous or cellular polypus and the vesicular polypus. He grouped them with similar polypoid growths in the nasal cavities, the large intestine, bladder and uterus, and believed they were the result of inflammatory irritation, though a congenital factor might exist in some cases. He also recognized that malignant transformation may take place.

Ebstein (1864) divided gastric polypi into the pedunculated and nonpedunculated; into those occurring in groups and those in isolated growths. Brissaud (1885) classified polypi as polyadenomata, but this term is correct only insofar as it is applied to benign tumors arising from mucosal epithelium.

Ewald described polypoid growths as a result of chronic gastroadenitis. He refers to a drawing of Cruveilhier's "in which the polypoid growths hung down from the mucous membrane like the teats of a young puppy."

Chiari (1888) reported a case of gastric intussusception due to a group of polypi near the pylorus escaping through the opening into the duodenum and producing partial obstruction. Cornil also reported a case of pyloric obstruction. In Myer's case a mass of polypi obstructed the pylorus and the patient died from hemorrhage 3 days after their removal by operation. As they are quite vascular, it is readily understood that they may swell when subjected to irritation or constriction.

Ménétrier's investigation of gastric polypi, published in 1888, marked an important step in advance. He accepted Brissaud's designation of polyadenomata and divided them into two classes: (*a*) Les *polyadenomes polypeux*, which he believed developed from

the superficial; (*b*) the flat or fanshaped *polyadenomes en nappe*, which developed from the deeper portion of the glands. He believed they were the result of chronic gastritis.

Before considering the etiology, pathology and clinical course of the two classes of polyadenomata described by Mènètrier, it should be emphasized that benign polypi of the gastrointestinal tract, arising from other tissues than the superficial or the gland epithelium of the mucosa, should be excluded from the discussion. If we accept the contention of Borrmann and others, the single adenomatous polypus should be included in the same group as the multiple, as they arise in the same way and show a similar tendency to carcinomatous transformation, and the papillomatous polypus would also be included as it arises from mucosal epithelium. The polyadenomata, then, would constitute a definite group of epithelial origin, arising from or under the mucous membrane, exposed to the irritations and inflammatory reactions affecting the mucous membrane, and further characterized by their liability to undergo cancerous transformation. The only thing they have in common with other benign polypoid tumors is their liability to produce certain mechanical symptoms, as has already been mentioned. Moreover, the myomata, fibromata, lipomata and other tumors, not of epithelial origin, more often project from the outer than from the inner walls of the gastrointestinal tract, so that inflammatory irritation of the latter obviously does not enter into the question of their causation as it does with polypi of epithelial origin.

In discussing the polypi of epithelial origin—the solitary and multiple adenomatous polypi and the papillomata—it is necessary to consider their causation and their relationship to inflammatory hyperplasia of the mucous membrane.

In common with most of the older writers, Ménétrier believed that gastric polyadenomata are the result of chronic gastritis and the inflammatory origin is still upheld by many authorities, including Ewing, Hektoen and Riesman, Versé, Konjetzny, Lubarsch, Hauser and other pathologists. Clinicians have inclined to the inflammatory theory, as suggested by the terms gastritis and colitis polyposa.

Others, following the teaching of Cohnheim, emphasize the importance of congenital tissue rests, or *anlage*, or perhaps some hereditary abnormality of the epithelium. They bring forward many arguments against the inflammatory theory, among others the occurrence of polypi in the comparatively young when there has been no antecedent inflammation; the existence of polypi for many years without symptoms; the frequency of chronic inflammatory conditions involving the gastrointestinal mucous membrane without polypoid formation; that chronic gastritis, as a rule, tends to atrophy rather than to hyperplasia of the glandular tissue; that

in solitary adenomatous polypi the growth arises abruptly from the mucous coat without evidence of inflammatory reaction in the surrounding tissues, and that the type of epithelial reaction and its relation to the underlying connective tissues in true adenomatous polypi differs from that of inflammatory hyperplasia. They maintain that the inflammatory reaction associated with adenomatous polypi may be a secondary phenomenon due to irritation produced by the growth.

On the other hand, some authorities who emphasize the paramount importance of the congenital factor admit that inflammatory irritation may act as an exciting or releasing cause for producing tumor activity in tissue rests. A Brunnerian type of polypus of the stomach has been described by Hayem, consisting of a glandular structure analogous to that of the duodenal glands. Konjetzny and Versé claim to have traced a direct and gradual continuity from chronic gastritis to mucous membrane hyperplasia, polyposis and cancer. In 12 cases of early gastric carcinoma found incidentally at autopsy in patients dying of other diseases Versè noted flat or papillary or polypoid thickening of the mucosa, and in several of them hyperplastic or atrophic gastritis. Ewing attaches slight importance to developmental anomalies, and states that in some cases carcinoma is associated with general hypertrophic gastritis, in others with a focal gastritis. Hayem describes diffuse scirrhus carcinoma developing from a diffuse parenchymatous gastritis, and cancer is known to develop frequently in the scars of gastric ulcer. Fibiger and Wassink claim to have produced gastric polyposis by the experimental feeding of a species of nematode, and Ishibashi and Otani by the application of coal tar. In Dukes' experiments with the application of tar to mice the sequence, though not invariable, was hyperplasia, papilloma, epithelioma.

Both the congenital and the inflammatory factors appear to be important and may be coördinated by accepting the one as a primary and the other as a releasing factor. Those who accept this view believe that inflammatory irritation can produce adenomatous polypi only in the presence of epithelial rests, and that inflammatory hyperplasia of the mucous membrane and the type of polypoid condition ordinarily accompanying it should be considered a different type of formation from that of true adenomata. Borst and other authorities, however, admit the difficulty of sharply differentiating the two conditions. Whether acting primarily or secondarily, it is probable that inflammatory irritation is very important in its relation both to the adenomata and carcinomata.

Scherer, from a study of 4 cases of massive folding of the gastric mucosa (Riesenfaltenbildung) found incidentally at autopsy, emphasizes the congenital factor, often associated with developmental defects or anomalies in other parts of the body: "Es handelt sich bei unseren Falten demnach um echten kongenitalen

partiellen Riesenwuchs." Inflammation and nervous or hormonal influences, he believes, may be releasing factors.

Gastric adenomatous polypi occur more frequently than has been supposed, even though many recent textbooks and systems of medicine do not mention them. Osler states that gastric polypi (polyadenomata) are common. Ebstein reported 14 cases of gastric polypi, 12 single and 2 multiple, in 600 autopsies. Eliason and Wright, in 8000 autopsies in the Philadelphia and University of Pennsylvania Hospitals, state that polypi were found in 32 per cent of gastric tumor cases, though only 1 case of polyposis was observed. Other pathologists and clinicians have found gastric polypi much less frequently. Thus Tilger reports only 14 cases in 35,000 autopsies; Chrosrojeff, in the Obruchow Krankenhaus, 4 cases in 7500 autopsies; Meulengracht, of Bremen, 11 cases in 11,475 autopsies. In the Mayo Clinic Balfour's case was the only one observed in 8000 gastric operations up until 1919, and Carman had recognized only 2 cases in 50,000 radiologic examinations; but Balfour and Henderson, in 1927, reported 58 cases of benign tumor of the stomach, 14 of which were fibroadenomatous polyps, 4 adenomas, 1 papilloma, 4 cases of polyposis and 2 of hypertrophied mucosa.

Dukes carefully examined 127 intestines from cecum to sigmoid and found simple tumors in nearly 10 per cent, and in 33 consecutive cases of cancer of the rectum adenomatous tumors were found in 25.

It is evident that exclusion of the polypoid growths of hyperplasia from the adenomatous group will be reflected in the statistical estimations of various authorities. Those who include the inflammatory polypoid growths of hyperplasia will find polypi comparatively frequently, while those who include only the true adenomatous polypi will find them rarely. The diversity of opinion among authors as to frequency is, therefore, accounted for by the conditions which different observers include within the term polypi or polyposis. Brunn and Pearl succeeded in collecting 84 cases of gastric polyposis up to 1926, and several others have been reported since that time.

In an experience of some 2000 autopsies in Toronto in hospital and private practice, one of us (Anderson) has met with a case each of multiple cysts of the stomach and intestines, *polyadenoma en nappe* of the stomach, benign adenoma of the duodenum, myxoma of the upper part of the jejunum, 1 of lipoma and 1 of myoma of the outer wall of the colon; 3 cases of polyposis of the colon and 1 of a large adenomatous polypus of the rectum in a boy, aged 17 years, producing obstruction.

Wegele made the first antemortem diagnosis of polyposis ventriculi at operation, in 1909, and Balfour's case was the first diagnosed by radiographic examination. In 1913 J. A. Myer reported a case in America in which he encountered at operation a mass of

polypi producing pyloric obstruction; in 1921 Alex. Macphedran reported a case of gastric polyposis in a woman, aged 50 years, who had suffered for years from epigastric discomfort after meals, diagnosed by radiographic examination (Dr. Dickson). Schindler, of Münich, reported a case, in 1922, diagnosed by gastroscopy.

The fact that polypi may exist for many years without symptoms, or with symptoms of digestive disturbance neither definite, characteristic nor uniform, probably accounts for their frequently being overlooked. As a rule, no tumor mass can be palpated, though there may be a sense of increased resistance over the epigastrium. Even at operation the condition may not be recognized unless the stomach is opened and its interior explored. How readily this may occur is illustrated by a patient, a woman, aged 40 years, who had suffered for years from symptoms suggestive of duodenal ulcer. Her abdomen had been opened on two occasions by experienced and competent Toronto surgeons and nothing found. Dr. L. G. Cole, of New York, after radiographic examination, concluded she had gall stones, though the clinical evidence pointed more to the duodenum as the seat of the trouble. As she suffered from intermittent obstructive symptoms she was referred to Dr. H. A. Bruce, in 1914, for operation and investigation of the gall bladder duodenal area. He found a shaggy, adenomatous tumor, 12 cm. long, 7 cm. wide and 3 cm. thick, attached to the interior of the first part of the duodenum by a thin pedicle some 5 cm. in width. (Fig. 1.)

The mass was easily removed and the patient made an excellent recovery. The radiographic plates in this case were misleading from the fact that the barium, caught in the interstices of the tumor threw shadows simulating multiple biliary calculi. An interesting feature of this case was the intermittent character of the symptoms, exacerbations evidently being due to occasional vascular engorgement and swelling of the tumor producing partial obstruction.

As the gastrointestinal adenomatous tumors eventually undergo carcinomatous transformation in 45 to 60 per cent of cases (Doering, Wechselmann, Meulengracht), no doubt the condition has often been mistaken for primary carcinoma. Mills, however, found malignant degeneration in only 20 per cent of 20 cases, and Brunn and Pearl in only 12 per cent of their collected cases. These percentages, like other statistical figures, will obviously vary with the conditions included within the term polypi or polyposis. Stewart, in 11,000 autopsies in Leeds General Infirmary, found gastric polypi in 47 and 13 out of 263 cases of cancer of the stomach, or 4.9 per cent, originated in polypi.

The symptoms associated with polypi will vary according to their size, number, location and structure, and also in relation to preceding or associated diseases. The mechanical symptoms are produced especially by pressure, traction and partial or complete

occlusion of orifices or lumen of the tract and may be intermittent or continuous.

In the small number of adenomatous gastric polypi reported, absence of free hydrochloric acid has been a prominent symptom and this is suggestive of widespread changes in the glands such as occur in gastritis with atrophy. As polypi may exist for years without symptoms, we have no knowledge as to how early the achylia develops; it is not a constant symptom, and one would scarcely expect to find it in the case of single or few polypi with otherwise normal mucosa. Cases with achylia may present an intractable diarrhea. These considerations apply equally to the presence of egg-white mucus in the stomach contents, which has frequently been referred to as a symptom of polyposis. Severe hemorrhage or occult bleeding has been noted in some 40 per cent of cases and is similar to that occurring in papillomata of the bladder.

Anemia is usually mentioned as an important symptom and may be explained by loss of blood, interference with digestion or atrophic changes in the glands. Balfour and Henderson emphasize its importance and refer to 1 case diagnosed as pernicious anemia. In 3 out of 8 cases which had undergone carcinomatous transformation, reported by Miller, Eliason and Wright, a diagnosis of pernicious anemia had been made.

Microscopic examination of pieces of tissue obtained from stomach contents or feces may assist in diagnosis, though this measure is uncertain unless the tissue is large enough to show submucosal infiltration.

As pointed out by Carman, Ruggles and others, radiologic examination is not an infallible means of diagnosis, though undoubtedly it is the most important. It is likely to be of most value where the polypoid condition is widespread, deforming the gastric outline or associated with obstructive symptoms. Ruggles (quoted by Brunn and Pearl) states: "Just as in the pathologic picture, so in the roentgenograms there are borderline cases in which one cannot differentiate between hypertrophic rugæ resulting from chronic gastritis and polyposis." It is of value in the diagnosis of ulcer, gall stones and other associated conditions, and no doubt will be of assistance more frequently in the future than it has been in the past. It is of less use in the case of solitary polypi, especially if not causing mechanical symptoms or before carcinomatous transformation.

According to Moore, "Multiplicity of the growths, as evidenced by multiple internal filling defects, is strongly indicative of benignity. In classic examples of diffuse polyposis the gastric shadow *has the appearance of a coarse sponge*, because of the numerous oval or rounded translucences. The stomach is of normal size, the line of the curvatures is usually traceable, *although it may be serrated*, and

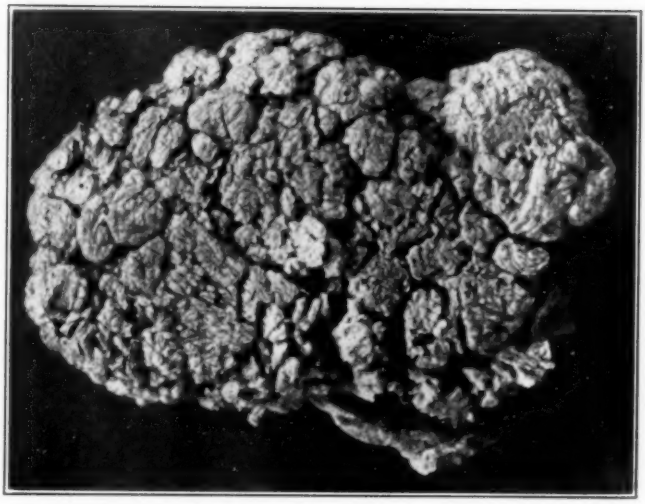

FIG. 1.—Pediculated adenoma of the duodenum.

FIG. 2.—Case 1. R. L. M., aged 49 years. Gastric polyposis.

FIG. 3.—Case 2. Mrs. H. W., aged 54 years. Suspected gastric polyposis.

FIG. 4.—Case 3. Mrs. G. B., aged 37 years. Suspected gastric polyposis.

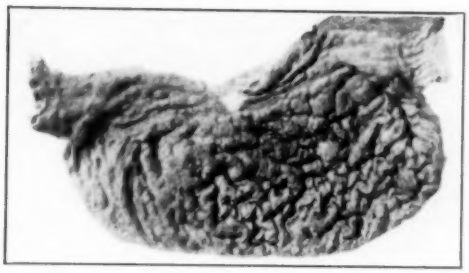

FIG. 5.—Leukemic deposit in the stomach wall, presenting gross appearance of polyadenoma en nappe.

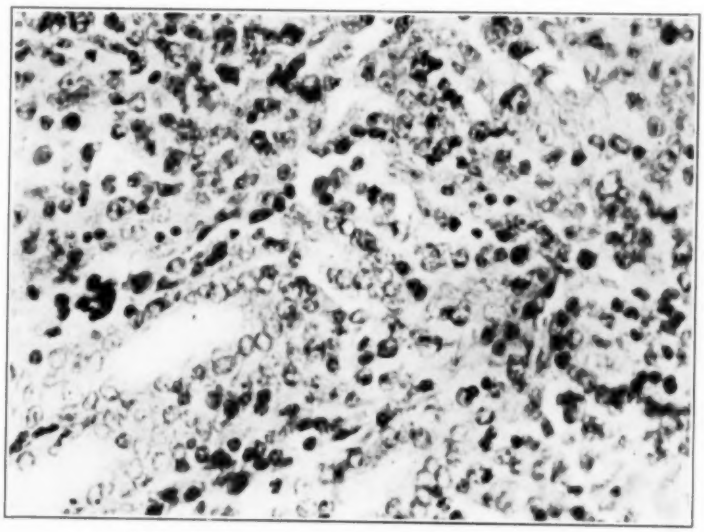

FIG. 6.—Histologic section of leukemic stomach.

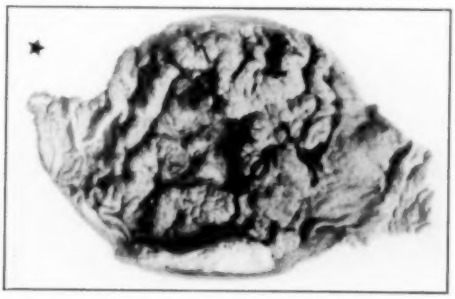

FIG. 7.—Adeno-carcinoma of the stomach developing in the center of an area of polyadenoma en nappe.

peristalsis runs its ordinary course. As a whole, the picture is striking and distinctive."

The cases reported in this paper present an interesting and generally uniform series of radiologic findings. On the screen the greater curvature showed serrated irregularities which could be obliterated by pressure, yet this pressure caused more pronounced irregularities in different portions due to the barium being forced in between the rugæ, and, further, with the patient placed in different positions and no pressure exerted, other irregularities were observed. Peristalsis was noted to pass through the involved areas, though somewhat diminished, especially so in Case 1 (Fig 2). No palpable mass could be felt, yet in Case 1 a soft fullness was elicited over the involved area. The plates all showed the same serrated irregularities as described on the screen with the addition that variations of density and irregular streakings were noted in the adjacent parts of the stomach. This mottling and streaking and serrated contour varied on the different plates of the same series. All showed a ground wave of peristalsis passing along the greater and lesser curvatures. There was no constant stiffening in any one part. In Case 1 peristalsis was diminished over the involved area. All 3 showed the greater curvature to be involved. In studying these cases over a period of time serial variations occurred which corresponded closely to the clinical condition of the patient. The diagnosis of the condition is important from the viewpoint of treatment, as subtotal gastrectomy is the most satisfactory procedure if the extent of involvement and the patient's condition permit of its being done. It has been carried out successfully in 2 cases reported by Strauss, Meyer and Bloom.

Case Reports. CASE 1.—November 28, 1928 (Fig. 2). R. L. M., aged 49 years, weighed 145 pounds (maximum) and 121 pounds (present), chemist, had had no serious illness in childhood and none in adult life except pneumonia 20 years ago, with good recovery, and hemorrhoids, with successful operative treatment, before he was accepted for overseas service, June, 1917.

He went to France with the infantry, March, 1918, and was in the operations about Amiens. In June, 1918, he reported to his medical officer, complaining of loss of appetite, "water brash" and constipation, and this continued more or less until August, when he developed pyrexia of unknown origin, and was sent to the Casualty Clearing Station, August 27, to Le Treport, August 30, and then to Bassingstoke for 3 or 4 months. He was suffering from serious obscure digestive trouble—epigastric pains, nausea, vomiting, some belching and pain usually about an hour after food. From 1920 to 1927 he was employed in a drugstore and occasionally was off for a week or two complaining of epigastric pains; he felt exhausted, nervous, irritable, apprehensive and suffered from frontal, occipital and temporal headaches; "felt floored and done up." His digestive trouble grew worse—epigastric pains, flatulency, constipation, nausea and vomiting immediately after eating or drinking. He finally gave up work, October 23, 1927, and was under the care of J. G. Lee, who diagnosed duodenal ulcer. Radiologic examination (Tovell) showed evidence of gastric polyposis, the duodenum

not being visualized. He became reduced in weight to 93 pounds. In January, 1928, he began to improve, but had a recurrence of obstructive symptoms, with nausea and vomiting in March, 1928, and was put back on Sippy diet.

He is small, thin, of nervous type; color good; has improved in health sufficiently to undertake part-time work. He has no nausea or vomiting at present but "water brash;" epigastric discomfort usually when the stomach is empty; feels bloated after meals; bowels constipated; on abdominal examination no tumor is felt, but some tenderness and sense of increased resistance over epigastrium; physical examination otherwise of no special importance. Blood pressure, 90 systolic and 60 diastolic.

During the winter of 1929 he had recurrent attacks of "water brash," persistent epigastric soreness, bloating and occasional vomiting after meals; stools dark at times apart from taking medicine; sensitiveness and increased resistance over epigastric area.

Examination of Stomach Contents After Ewald Breakfast. December 15, 1928: 200 cc. of sour material; free acid, 60; total acid, 100; occult blood (bezidin), negative. March 21, 1929: Free acid, 80; total acid, 100; occult blood (bezidin), negative.

Examination of the Blood. Hemoglobin, 95 per cent. The red blood cells were of good size and shape and there is no leukocytosis. A differential count of the stained smear showed the following percentages of white blood cells: Polymorphonuclears, 45; lymphocytes, 39; transitionals, 9; eosinophils, 3; large mononuclears, 3; basophils, 2.

The Wassermann reaction was negative.

The urinalysis gave normal findings.

Gastrointestinal Radiologic Report. October 26, 1927 (Tovell): *Screen.* The meal passed through the esophagus without any evidence of obstruction. The stomach filled. Peristaltic waves were present and passed to the pylorus. The greater curvature was extremely rough and irregular in outline, but under manipulation could be indented. The stomach was freely movable.

Plates. The plates show evidence of marked roughening and irregularity involving the whole of the greater curvature extending from the cardiac end almost to the pylorus. The lesser curvature does not show any extensive change. There appears to be evidence of peristalsis noted on the greater curvature. There is no persistent deformity such as one would expect to find if carcinoma were present. The first portion of the duodenum seems to be fairly well filled on one of the plates.

Six Hours Screen. The stomach was empty. The meal occupied the cecum and terminal ileum. Both were independently movable. There was no obstruction to the small bowel.

Conclusions. From the examination there is evidence of marked deformity involving the stomach, particularly the greater curvature, suggestive of polyposis. There is no evidence of growth involving the colon.

In all, 7 radiologic examinations have been made at varying intervals, and while the gastric indentations varied from time to time, in general the deformities were the same.

In this case the presence of hyperchlorhydria and the absence of egg-white mucus in the gastric contents is against the diagnosis of polyposis. The question arises whether the radiologic findings are sufficient to warrant the diagnosis.

January 30, 1931: This patient has been under observation 3 years and 5 months since the first radiologic examination, and continues in fairly good health.

CASE 2.—May 10, 1928 (Fig. 3). Mrs. H. W., aged 54 years, 5 feet 6 inches in height, weighed 155 pounds (maximum) and 118 pounds (present). Family history: Her maternal grandfather probably had myxedema her mother died of myxedema at 45 years, two sisters developed myxedema after childbirth and her only son's appearance suggests Fröhlich's syndrome. She is ordinarily vigorous and active. She had inflammatory rheumatism at 16 years; recovered, but had a recurrence after coming to Toronto, in 1902. She had four attacks of hematemesis, the first as a girl, the last some 20 years ago, after her husband's sudden death. She has suffered more or less for years from rheumatic manifestations, especially in the fingers, shoulders, back and hips. The bowels are constipated and there has been more or less indefinite digestive disturbance for years. She has three devitalized teeth and fairly marked chronic tonsillar infection; some chronic bronchitis, scattered, sibilant and moist râles; slight cough and thick greenish-yellow morning expectorations. No tubercle bacilli were found in the sputum. Temperature was normal. The blood pressure was 100 systolic and 66 diastolic. The heart was normal. The abdomen was scaphoid, with marked gastric succussion splash to below the navel; there was "squashiness" over the cecum and some sensitiveness below and to left of the navel. The patient is definitely hypothyroid and is taking thyroid extract.

Laboratory examinations included: Negative urinalysis.

The Wassermann reaction was negative.

The blood count showed: Hemoglobin, 90 to 95 per cent; red blood cells, 4,800,000; color index, 0.9; white blood cells, 9000. The red blood cells are of good size and shape and a differential count of the stained smear shows the following percentages: Polymorphonuclears, 51; lymphocytes, 46; eosinophils, 2; basophilis, 1.

Radiologic examination showed evidences of an old duodenal ulcer without gastric stasis. There is marked irregularity of the greater curvature both on screen and plates, suggestive of polyposis.

October 4, 1928: After clearing up oral infection, tonsillar enucleation and 2 months' holiday the patient was much better and had gained 7 pounds in weight.

The question arises again in this case as to the interpretation of the radiologic plates. Does the irregularity of the greater curvature warrant the diagnosis of polyposis and recourse to operation? Further clinical and radiologic study, checked by surgical and autopsy experience of such cases, is evidently required, and in the meantime the procedure adopted should be determined by clinical developments. After nearly 3 years this patient's condition has materially improved.

CASE 3.—January 25, 1929: Mrs. G. B., aged 37 years, weighed 135 pounds (maximum) and 94 pounds (present). Ordinarily active and vigorous, of nervous temperament, she has had no serious illness except albuminuria with her last pregnancy, 14 years ago. During the past 18 years she has suffered from belching of gas; severe epigastric pain at times, not related to time of eating or character of food; no nausea or vomiting; bowels regular and free; moderate pyorrhea about the remaining nineteen teeth; moderate chronic tonsillar infection; occasional sore throat. In recent years she has suffered from lumbago and sciatica. Heart and lungs showed nothing abnormal on physical examination. Blood pressure, 100 systolic and 74 diastolic. In the abdomen there was well-marked

epigastric "squashiness;" no definite tenderness but a sense of increased resistance toward pylorus.

Laboratory findings included:

Negative urinalysis.

The Wassermann reaction was negative.

The blood count showed fairly marked secondary anemia; hemoglobin, 80 per cent; red blood cells, 4,800,000; white blood cells, 9000. Differential count percentages showed: Polymorphonuclears, 61; lymphocytes, 36; Eosinophils, 2; transitionals, 1.

Radiologic Examination. January 26, 1929 (Tovell): The stomach filled. Peristaltic waves were present and passed to the pylorus both on the greater and lesser curvature. The greater curvature showed slight irregularities in the dependent portion extending to the pylorus. These irregularities were more accentuated in the prone position. On inspiration the greater curvature passed downward, filling fairly well, except for several serrated deformities near the pylorus. No palpable mass was elicited. The duodenum was normal.

Plate. The plate confirms the observations made on the screen and showed the same irregularities, which are not due to spinal pressure. In the lateral position they are quite distinct.

Six Hours Screen. About $1\frac{1}{2}$ ounces remained in the stomach at the end of 6 hours.

April 3, 1929: Reëxamination showed evidence of the irregularities formerly described.

Plates. The plates confirm the observations on the screen and show the irregularities to be outside the region of spinal pressure and not so pronounced as on the first examination. There was no evidence of retention.

There is no radiographic evidence of ulceration or malignancy involving the stomach or duodenum. The defects noted on the screen and plates are strongly suggestive of polyposis. The changes are mostly on the greater curvature in the pyloric region.

In the 2 years since this patient came under observation her condition has improved.

April 8, 1929 (Fig. 4). The patient's condition is much improved after removal of infected teeth; she has gained 6 pounds in weight; rheumatic pains have disappeared; anemia is less marked; digestion much better; tonsils are definitely infected.

Blood findings were as on the previous examination, except for a slightly increased hemoglobin content.

Stomach contents after Ewald test breakfast: Free acid, 22; total acid, 41; occult blood (benzidin), negative.

In this case there was absence of egg-white mucus in the stomach contents, and free hydrochloric acid and total acidity were normal. While the radiologic findings are suggestive, one does not feel that, with our present knowledge, they are sufficiently conclusive to warrant an assured diagnosis of polyposis and surgical treatment.

A specimen in the University of Toronto Pathologic Museum of marked thickening of the gastric and intestinal mucosa, was obtained from a soldier, aged 68 years, who has been ill for over 2 years with ecchymoses about the eyes, forearms and chest; diarrhea with blood, abdominal pain and distention, weakness and anemia. The blood showed a typical condition of a chronic splenomyelogenous leukemia. The interglandular structure of the stomach and intestine was found infiltrated by myelocytes; there

was general lymph node enlargement. The specimen is interesting from the fact that the gross appearance is very similar to that of *polyadenoma en nappe*. A gastrointestinal radiologic examination was not made, and one can only speculate as to whether this would not have been a case in which the radiologic findings would be difficult to differentiate from diffuse polyposis.

Another specimen (Fig. 7) in the University of Toronto Pathologic Museum presents the gross appearance of *polyadenoma en nappe*, with an ulcerated area of malignant degeneration in its center. It was obtained from a patient, E. L., aged 50 years, male, who had suffered from abdominal discomfort for some months before consulting his physician in August, 1923. At this time a radiologic examination suggested a large benign ulcer of the lesser curvature of the stomach. At operation the condition was thought to be carcinoma and a gastroenterostomy was done. Radiologic examination 3 months after operation was negative. The patient continued very well until March, 1924, when gastric symptoms recurred. A radiologic examination at this time again suggested gastric ulcer. At operation a gastric carcinoma was found, but too extensive for removal. The patient died, April 24, 1924, and at autopsy the whole mucous membrane except the pyloric antrum was thrown into large irregular folds or polypoid masses resembling the convolutions of the brain. Sections from the central ulcerated area showed a carcinomatous structure—columns and groups of atypical epithelial cells supported by delicate stroma.

The gross appearance of the specimen suggests *polyadenoma en nappe*, with secondary carcinomatous transformation. In view of the condition found at autopsy, it is difficult to understand the radiologic findings. It is scarcely possible that the diffuse polypoid condition developed subsequent to the radiologic examination some 6 weeks previous to death. If it existed before that time and was not revealed by the examination, then radiologic diagnosis cannot always be depended upon to demonstrate the condition, and negative radiologic findings do not necessarily exclude the possibility of polyposis.

Summary. 1. The literature on polypi and polypoid conditions of the gastrointestinal tract is reviewed, and their etiology, symptomatology, radiology, pathology and relationship to carcinoma discussed.

2. Three cases of gastrointestinal disease with peculiar radiographic findings suggestive of polyposis are reported, and their progress over a period of two years or more reported. The question as to whether a diagnosis of polyposis is warranted on the radiologic findings is discussed and also the advisability of surgical treatment.

3. An unusual case of polypoid tumor of the duodenum is described.

4. A specimen of leukemic hyperplasia of the gastric mucosa is

presented with gross appearance suggestive of that of *polyadenoma en nappe*.

5. A specimen of *polyadenoma en nappe* with cancerous transformation is described.

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BRITTAIN'S PATHOGNOMONIC SIGN OF GANGRENOUS APPENDICITIS.

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In many patients in whom the diagnosis of appendicitis was not made before operation the disease has been found to exist when the abdomen was opened. On the other hand, there have been many

cases in which, though everyone was quite positive of the diagnosis of appendicitis before operation, the appendix was found to be either normal, trivially, chronically or pre-pathologically diseased.

Most surgeons of experience are quite willing to admit that in many cases there are numerous errors in predicting the exact type of lesion to be found in a given case at a given moment. For this reason experienced doctors are prone to urge, on the one hand, immediate operation in every case and, on the other hand, a reasonable delay for longer observation. The practical effect is that we have often found the appendix to be gangrenous when that was unsuspected, and we have often found the appendix to be normal or slightly diseased in cases in whom it was deemed wise to perform an emergency operation upon first sight.

In July, 1928, Dr. R. Brittain, an intern in the Richmond Memorial Hospital, was examining with me a young man in whom there was no doubt that he needed prompt operation for appendicitis. Upon palpation of the abdominal wall there was noted, in addition to tenderness and spastic rigidity of the overlying muscles, that the right testicle was suddenly retracted to the upper part of the scrotum. Repeated examination showed that this invariably occurred whenever the lower right quadrant was palpated, and the testicle remained retracted as long as the pressure was made. Upon relief of pressure, the testicle immediately dropped to its original position.

Operation revealed that the appendix was gangrenous, the peritoneum fiery red and the cavity contained amber-colored exudate in this region.

We had never observed this phenomenon before, and upon questioning a great many doctors and surgeons in the community we could find no one who had made the observation.

From this time we began to look for the sign in every case of appendicitis and of other conditions bearing resemblance in symptomology to this disease. We have now observed it in nearly 500 cases of gangrenous appendicitis and have failed to observe it in more than 300 other acute abdominal affections, such as intestinal obstruction, gall bladder and ulcer diseases, kidney and ureteral colic, and nonsurgical affections, such as functional colicky pains, following dietetic indiscretions and the taking of purgative medicines.

For more than 2 years now, since the observation of the first 100 cases, we have come to look upon the sign as pathognomonic of gangrenous appendicitis, and proceed to operate upon the patient without further delay. On the other hand, when the sign is absent we have felt quite sure, and this has been substantiated by operation, that the disease, if appendicitis at all, is not gangrenous, and do not hesitate to defer operation for further study.

During our observations, before we had had sufficient experience to feel justified in acting upon our tentative conclusion of the

value of this sign, we operated upon a few patients in whom we believed appendicitis to exist, and in whom we found the appendix was normal. One striking case of this was the case of a little boy, who had abdominal pain for 48 hours, together with vomiting, tenderness, and even the indication of a small mass which we thought was a small appendiceal abscess. He did not have Brittain's sign, and before operation we announced that we might have been pinning too much faith upon the sign. Operation revealed that the boy had intussusception of the small bowel, with complete mechanical obstruction, and a normal appendix.

There have been a few other errors of observation and interpretation of the sign. In one of the earlier cases, in a man nearly 70 years of age, the retraction was so slight that we were not sure it existed. We found at operation next morning a gangrenous appendix. In many cases, however, since this one, we have noted the sign in patients as old as 65 years, and just recently in a man aged 76 years; though one can easily imagine the retraction in such cases could rarely be so active as in younger men.

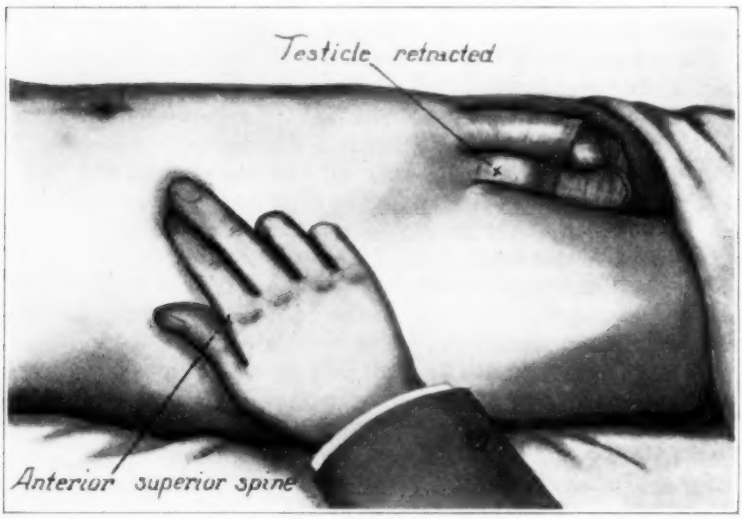
We made an important observation in one case in which by pressure exactly at the outer edge of the right rectus muscle exactly at the line of the umbilicus the right testicle retracted conspicuously. This was not interpreted as Brittain's sign. There was no retraction, no rigidity and no tenderness upon pressure in the right lower quadrant. There was some question of gall bladder disease. Roentgen ray showed bone changes in the spine, possibly a product of arthritis. Exploratory operation showed nothing abnormal in the abdomen. Could the tenderness and testicle retraction elicited by pressure exactly at the site of entrance of a nerve into the rectus muscle have been the result of neuritis incident to spinal arthritis?

In young children the testicles retract so easily that it is easy to be deceived in believing the sign is present when it is not. We have noted, however, that normal retraction influences both testicles (is not confined to the right side), and this is of differential diagnostic value.

In widespread peritonitis secondary to perforating ulcer of 24 hours or longer duration the testicle may be pulled up into an abnormally high position independently of pressure, and retained, *i.e.*, it does not come higher when pressure is made and does not go down when the palpating hand is removed. We note, therefore, that the sign of appendicitis involves both phenomena, namely, retraction upward when a palpating hand is applied, and return downward when pressure is removed. The sign is not influenced by morphin.

A certain technique in making the examination is necessary. The patient should be quietly at rest, the bedclothes pulled well down, a careful inspection made before the examining hand is applied and the patient's mind diverted from the test. Careful

palpation of the left side and upper abdomen is made before the right lower quadrant is touched. Then, upon a gentle touch of the lower right quadrant, especially at the McBurney area, as soon as the finger is applied the testicle is seen to retract upward. As long as the finger is held in contact the testicle remains in this position. As soon as it is removed the testicle will drop back to its original position.



Showing the retraction of the testicle when pressure is made on McBurney's point, in a case of gangrenous appendicitis. The testicle is normally located in the area surrounded by the dotted line.

It has been observed in some cases that, with the hand remaining gently on the abdominal wall, the testicle may drop back to its original position and then upon the removal of the finger will again retract (rebound retraction).

We thought for a while that in cases of gangrenous appendicitis located high up behind the cecum the sign might not appear or be less active. Further observation showed that it was present even in these cases, though it was less noticeable when pressure was made at McBurney's point than when pressure was made slightly higher toward the loin.

Now, with ample experience in the differential diagnosis between appendicitis and the other diseases with which we have so often found difficulty and made errors, we feel it desirable to present this sign to the profession, and have named it in honor of the young man who first noticed it, Brittain's sign.

The explanation of this phenomenon will still have to be theoretical. We assume that it is a manifestation of muscular contrac-

tion involving the internal oblique and its cremaster portion, which surrounds the spermatic cord and draws the testicle up. This is commonly explained upon the same basis as is the contraction of the right rectus muscle and the external oblique, by the transmission of the impulse from the point of irritation (the appendix and peritoneum) to the spinal cord and back over the motor nerves of the reflex arc to the muscles of the abdominal wall and the spermatic cord.

Summary. In the presence of gangrenous appendicitis palpation of the lower right quadrant of the abdomen invariably produces sudden retraction of the right testicle, which drops to its original position as soon as pressure is withdrawn.

The constant presence of this sign, first observed by Dr. Brittain, in 1928, in nearly 500 cases of gangrenous appendicitis, and its absence in more than 300 other acute abdominal conditions, make it, we believe, pathognomonic for gangrenous appendicitis.

STUDIES IN COMPLETE HEART BLOCK.

I. THE CARDIAC OUTPUT AND THE PERIPHERAL CIRCULATORY MECHANISM.

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ALTHOUGH numerous clinical and electrocardiographic studies of complete auriculoventricular block have been published, less attention has been given to the physiologic changes in the hemodynamics of this condition. In recent years it has become increasingly recognized that abnormal functioning of the heart is frequently accompanied by changes in the peripheral circulatory mechanism. In spite of the fact that the methods available for studying the physiology of the circulation in man are often indirect and limited in applicability, significant results may be obtained when several procedures are carried out simultaneously in a series of cases.

Complete heart block is a clinical condition of not infrequent occurrence which is generally considered of serious prognostic significance but which may exist for many years without symptoms. In order to maintain normal bodily functions in this condition, in

the presence of the striking changes in the cardiac mechanism, it is probable that compensatory adjustments occur throughout the entire vascular system. These readjustments may be in the nature of an increase in the stroke output of the heart or of changes in the blood pressure, blood volume, oxygen transport by the blood or possibly in the peripheral vascular tone. The aim of this study was to determine the nature and extent of these circulatory adjustments.

Clinical Protocols. Studies were made on 5 patients with complete heart block who varied in age, extent of incapacity and objective signs of cardiac failure. As the clinical protocols are of importance in interpreting the observations, they are presented before the experimental data.

Case Reports. CASE I.—L. S., aged thirty-three years, male, Jewish newspaper reporter. As a child he had a throat infection which may have been diphtheria, but had never had syphilis or any rheumatic infection. For about ten years he had suffered from intermittent attacks of epigastric pain accompanied by considerable gas. Peptic ulcer was suspected, but it was considered more probable that his symptoms were due to gastric neurosis. Seven years ago a complete heart block was discovered during the course of a routine physical examination, which persisted to date. There had never been any cardiac symptoms in spite of the fact that the patient was very active physically—a long-distance swimmer and a gymnast.

The physical examination was essentially negative. There was no pulsation in the neck. The heart was not enlarged to percussion; the sounds were regular at a rate of 40 per minute and of good quality, although there was some variation in the intensity of the first sound. No murmurs were heard. There was no arteriosclerosis or edema. The systolic blood pressure was 128 and the diastolic 80. The lungs were normal. The Wassermann reaction of the blood was negative. A teleroentgenogram of the heart showed it to be normal in size and shape; under the fluoroscope the ventricular contraction appeared forcible, the contraction of the heart being about 1 cm. with each beat. Measurements of the heart shadow were 8.2 cm. to the right and 4.7 cm. to the left, giving a total transverse diameter of 12.9 cm. The internal diameter of the chest was 28.1 cm. Repeated electrocardiograms always showed complete heart block with an auricular rate of 60 and a ventricular rate of 40; the P–P intervals being slightly shorter when a ventricular complex fell between them. The Q–R–S complexes were normal and the T waves upright in all leads. The axis was normal.

Diagnosis. Complete heart block. Etiology questionable, possibly of congenital or diphtheritic origin. Gastric neurosis.

CASE II.—R. S., aged thirty-three years, colored housewife, in perfect health. She had never had diphtheria, syphilis or any rheumatic infection. Her slow heart rate was first noted nine years ago, during the course of a routine insurance examination and probably had persisted since. She had never had any cardiac symptoms, although she led an active life.

Physical examination was essentially negative. There was no pulsation in the neck. The left border of the heart was percussed 10 cm. to the left in the fifth costal interspace, 2 cm. outside the midclavicular line. The sounds were of good quality, regular, at a rate of 35 per minute. There was a variation in the character of the first sound both at the apex and base; sometimes it was loud and snapping, and at other times muffled. No murmurs were heard. The lungs were clear; there was no arteriosclerosis

or edema. The blood pressure was 115 systolic and 70 diastolic. The Wassermann reaction of the blood was negative. Teleroentgenogram measurements of the heart showed slight transverse enlargement. The heart show measured 8.9 cm. to the left and 4.9 cm. to the right, giving a total transverse diameter of 13.8 cm. The internal diameter of the chest was 24.1 cm. Fluoroscopic examination showed an increased ventricular excursion, the ventricle contracting 1 to 1.5 cm. with each beat. The electrocardiogram showed complete heart block, with an auricular rate of 75 and a ventricular rate of 35 per minute. The *Q–R–S* complexes were normal and the *T* waves upright in the first and second leads, but inverted in Lead III. There was left ventricular preponderance.

Diagnosis. Complete heart block of doubtful etiology, possibly congenital.

Case III.—O. L., aged seventy-eight years, Norwegian, janitor; entered the hospital with a complaint of dizziness and fainting. His past history was unimportant; he had never had diphtheria, syphilis or any rheumatic infection. One month before entry he began to be moderately dyspneic on exertion. Two weeks later he developed a dull pain beneath the left clavicle which came and went without relation to exertion. One week before entry he experienced a sudden transient attack of faintness and dizziness. Similar attacks recurred about twice daily until he entered the hospital. At that time he also noted slight orthopnea and edema of the ankles. Physical examination on entry showed a rather thin old man in no distress. There was a marked arcus senilis and moderate sclerosis of the fundal vessels of the eye. The heart borders could not be accurately determined. The sounds were regular at a rate of 38 and of fair quality. There were no murmurs. The aortic second sound was accentuated. There was moderate peripheral arteriosclerosis and slight edema of the ankles. The systolic blood pressure was 270 and the diastolic 80. The lungs were emphysematous, but otherwise negative. The Kahn reaction of the blood was negative. The urine showed a specific gravity of 1.015 to 1.020, and on repeated examination albumin ranged from none to a trace. There were occasional hyalin and granular casts.

The heart showed moderate transverse enlargement by roentgenogram, with a prominent left ventricle. The aorta was tortuous and calcified. Electrocardiogram showed complete heart block with an auricular rate of 90 and a ventricular rate of 40. The *Q–R–S* complexes were normal; the *T* waves were diphasic in the first lead and upright in the other two. The axis was normal. The patient was digitalized and kept in bed; he improved slightly, and the edema disappeared. His condition became stationary; he was quite comfortable in bed, but on exertion dyspnea and dizziness returned. Six weeks after entry the special clinical studies were made. A month later he had three marked Adams-Stokes attacks in one week. Four months after entry his dyspnea became somewhat worse; a month later he developed bronchopneumonia and died. Autopsy was not obtained.

Diagnosis. Complete heart block, etiology arteriosclerosis; arteriosclerotic heart disease.

Case IV.—M. G., aged fifty-eight years, American housewife, was admitted because of fainting spells. Her past history was unimportant; she had never had diphtheria, syphilis or any rheumatic infection. Two years before entry she began to be dyspneic on exertion, to tire easily and to have slight edema of the ankles. Her local physician told her she had high blood pressure and diabetes, and he limited her activity and her diet. Shortly after this she had her first fainting attack and subsequently had about twenty up to the time of entry to the hospital. All of her symptoms gradually increased in intensity.

Physical examination on entry showed a rather obese woman comfortable in bed. There was slight arteriosclerosis of the vessels of the eyegrounds. A venous pulsation at a rate of 90 was seen in the neck. The lungs were clear. The heart was enlarged, the left border being percussed 14.5 cm. in the fifth intercostal space. The sounds were of fair quality and regular at a rate of 30. There was a harsh systolic murmur, best heard in the second and third interspaces, transmitted to the neck with a systolic thrill. The aortic second sound was accentuated. The liver was palpated 4 cm. below the costal margin. There was slight edema of the ankles. The blood pressure was 240 systolic and 70 diastolic. The Kahn reaction of the blood was negative. The urine was negative except for a trace of sugar on entry; this disappeared under treatment.

Teleroentgenogram showed that the shape of the heart was consistent with a mitral deformity in the region of the left auricle and enlargement to the left. The measurements of the heart shadow were 13.4 cm. to the left and 5.2 cm. to the right. The total transverse diameter was 18.6 cm.; the internal diameter of the chest, 27 cm. The first electrocardiogram showed complete block, with an auricular rate of 90 and a ventricular rate of 30. The *Q–R–S* complexes were prolonged to 0.12 to 0.14 seconds and were slurred in all leads. The *T* waves were opposite the main deflection of the *Q–R–S* complex in each lead. The findings were typical of left bundle-branch block. A few days later another electrocardiogram resembled the preceding except that right bundle-branch block now existed. A possible explanation for the development of first left and then right bundle-branch block in successive electrocardiograms is that the origin of the impulse which excited the ventricular contraction was first in one branch of the bundle of His and subsequently shifted to the other branch.

With rest in bed the patient improved considerably. The edema cleared up, the liver diminished in size and she had no Adams-Stokes attacks during the six weeks she remained in the hospital. The studies reported here were performed about two weeks after entry. Her symptoms, however, soon recurred. She reëntered the hospital a month later, had repeated Adams-Stokes seizures of great severity, some relieved only by adrenalin, and finally died in such an attack. Autopsy was not obtained.

Diagnosis. Complete heart block, etiology arteriosclerosis; arteriosclerotic heart disease; aortic stenosis; bundle-branch block; diabetes mellitus.

Case V.—M. T., aged fifty-seven years, American housewife, who was admitted with a complaint of shortness of breath. She gave no history of diphtheria or syphilis and had been well until four years before entry, when she had an attack of a migratory polyarthritis with fever. Shortly afterwards she had several fainting spells and was under treatment for several weeks for heart trouble in this hospital. At this time an electrocardiogram showed partial heart block with a *P–R* interval of 0.28 seconds and a rate of 57. The patient then improved and felt fairly well until a year and a half before entry. After that time she had increasing edema and dyspnea on exertion and for several weeks was bed-ridden.

Physical examination on entry showed a dyspneic, cyanotic woman. The veins of the neck were somewhat congested. The lungs showed moderate dullness and râles at each base. The heart was greatly enlarged to the left. The sounds were regular and of rather poor quality at a rate of 36. Blowing systolic and middiastolic murmurs were heard at the apex, and a blowing diastolic murmur along the sternal border. No peripheral arteriosclerosis was noted. There were marked ascites and extensive anasarca. The systolic blood pressure was 210 and the diastolic 80.

The Kahn test of the blood was negative. Teleroentgenogram of the heart showed marked transverse enlargement and widening of the great vessels. An electrocardiogram showed complete heart block with a ven-

tricular rate of 37. No *P* waves were visible. The *Q-R-S* complexes measured 0.08 to 0.12 seconds and were slurred, probably due to intraventricular block. The *T* waves were flat in Lead I and inverted in Leads II and III. The axis was normal. With rest in bed the patient improved but slightly, and her condition then became stationary. The special studies were carried out ten weeks after admission, when her physical condition was but little better than it was on entry. She was discharged a few weeks later. While at home her symptoms persisted, gradually grew worse, and she died nine months later. No autopsy was obtained.

Diagnosis. Complete heart block, etiology rheumatic fever; rheumatic heart disease; mitral stenosis and regurgitation; aortic regurgitation; probably auricular fibrillation; intraventricular block; marked congestive heart failure.

Methods of Observation. The blood pressure was determined by a mercury sphygmomanometer; the vital capacity by a Collins spirometer. The circulation time was found by the histamin reaction method.[1] The cardiac output was estimated according to the technique of Field, Bock, Gildea and Lathrop.[2] The principle of this method is that first described by Fick whereby the carbon dioxid contents of the arterial and mixed venous bloods in the lungs are indirectly estimated from an analysis of respiratory gas samples. The heart output is then calculated by dividing the carbon dioxid excreted by the subject per minute by the difference between the arterial and mixed venous carbon dioxid contents. Seven alveolar and "virtual venous" gas samples were obtained for each determination. In one instance the acetylene method of Grollman[3] was also employed. The blood volume was calculated by the dye method.[4] The venous pressure was measured by the direct method of Moritz and Tabora,[5] except that the Eyster indirect technique[6] was employed with Case V. In our experience the results obtained by these two methods are comparable.

The metabolism of the first 4 patients was obtained by the Tissot method and of the fifth patient by a Collins spirometer. For the determination of the oxygen and carbon dioxid content of the blood samples were taken under oil from the cubital and femoral veins without stasis and from the femoral artery. The analyses were carried out according to the manometric method of Van Slyke.[7] Lactic acid determinations were made according to the technique of Friedemann, Cotonio and Shaffer.[8] All studies were made in the postabsorptive state in semirecumbent position.

Interpretation of Results. Tables I, II and III outline the results of these observations and give the averages and ranges for similar determinations obtained by us at various times on groups of normal individuals. Our normal figures agree closely with the findings of other investigators who used the same techniques.

The 5 patients studied showed clearly three grades of circulatory functional capacity. Cases I and II had no functional impairment whatever. Cases III and IV were compensated at rest at the time

TABLE I.—MEASUREMENTS OF THE ARTERIAL AND VENOUS BLOOD PRESSURES, THE RESPIRATORY EXCHANGE, THE RATE AND VELOCITY OF THE CIRCULATION, THE BASAL METABOLISM, THE BLOOD VOLUME AND HEMATOCRIT, AND THE VITAL CAPACITY.

Case.	Heart rate per min.	Arterial blood pressure, mm. Hg.		Venous pressure, mm. Hg.	Respiratory minute volume output, L.	Carbon dioxid tension, mm. Hg.			Carbon dioxid output per minute, cc.	Cardiac output per minute, L.	Cardiac output per 100 cc. O_2 consumption, L.	Cardiac output per beat, cc.	Basal metabolism.		Circulation rate, sec.	Blood volume.		Hematocrit, per cent.	Vital capacity, cc./sq. m.
		Systolic.	Diastolic.			Alveolar.	Virtual venous.	Difference.					Per cent.	Cal./hr./sq. m.		Cc.	Cc./sq. m.		
I (L. S.)	38	106	70	+ 4	7.2	42.7	50.2	7.5	157	5.09	2.8	139	−20	31.5	24	4025	2470	46	2800
					6.4	40.1	47.3	7.2	145	4.92	2.8	123	−22	30.6					
II (R. S.)	36	115	70	+ 2	6.0	36.9	43.1	6.2	147	5.62	3.1	156	−14	31.5	29	3425	2100	41	1530
					6.2	36.5	43.2	6.7	151	5.28	2.9	147	−12	31.9					
III (O. L.)	32	270	80	+ 3	8.1	33.0	39.5	6.5	138	4.55	2.4	142	− 4	34.1	...	3865	2350	35	1400
					8.4	32.5	39.6	7.1	154	4.60	2.3	141	− 2	34.9					
IV (M. G.)	29	240	70	0	5.8	37.5	43.0	5.5	138	5.82	3.2	200	− 1	34.8	47	3620	2430	42	1540
					5.7	37.4	44.3	6.9	139	4.69	2.6	156	− 1	34.7					
V (M. T.)	36	210	80	+14	..	..	..	..	..	..	..	..	−15	29.6					
Normal average	..	..	..	..	6.9	39.8	47.8	7.6	202	6.7	2.7	101	...	..	23	..	3278*	41*	2500
Normal range	..	..	..	+10	..	..	..	..	..	..	..	..	−15 to +15	..	15 to 30	..	2730 to 4040*	36 to 47*	

* Normal figures as given by Rowntree, Brown and Roth.[4]

of the investigation, but showed definite evidence of myocardial damage and developed symptoms on slight exertion. (Class 2b of the American Heart Association Classification.[10]) Case V remained decompensated even in bed. (Class 3.) By evaluating the observation on all 5 patients, therefore, it should be possible to show not only what physiologic changes the heart block in itself produces in the circulatory mechanism, but also what further changes may take place as the myocardial reserve is progressively diminished.

TABLE II.—THE CARDIAC OUTPUT IN CASE II AS MEASURED BY THE ACETYLENE METHOD.

Case.	Heart rate per min.	Arteriovenous O_2 difference, cc./L.	Oxygen consumption per min., cc.	Cardiac output per min., L.	Cardiac output per beat, cc.	Basal metabolism, per cent.
II (R. S.)	36	58.6	187	3.20	89	−9
	36	55.9	187	3.36	93	
Normal average*	...	59.3	...	3.88	60	

* Normal figures as given by Grollman.[9]

TABLE III.—MEASUREMENTS OF THE OXYGEN AND CARBON DIOXID ARTERIOVENOUS DIFFERENCES AND THE ARTERIAL SATURATION IN CASES I, IV AND V.

Case.	Arteriovenous difference.				Arterial.		
	Arm.		Leg.				
	Oxygen, vol.%	Carbon dioxid, vol.%	Oxygen, vol.%	Carbon dioxid, vol.%	Content, vol.%	Capacity, vol.%	Saturation, vol.%
I (L. S.)	3.35	3.27	5.23	3.16	18.44	19.13	96
IV (M. G.)	2.63	1.92	5.24	4.35	17.97	20.07	90
V (M. T.)	9.32	7.86	10.95	7.27	17.74	19.85	89
Normal average (13 cases)	3.61	4.95	3.30	5.31	...	19.40	93
Normal range	1 to 5	1.7 to 8.3	1 to 8	1.6 to 9.4	...	17.3 to 21.88	89 to 96

No attempt will be made to analyze the symptoms and physical signs of these patients. Such an analysis will be made from a larger series and published later.

Arterial Blood Pressure. Three of the patients showed the characteristic greatly elevated systolic and normal or low diastolic pressures which have often been noted in association with heart block. The 2 patients who had a normal arterial blood pressure were relatively young and without functional impairment, or evidence of organic myocarditis or peripheral arteriosclerosis. Possibly these 2 patients had elastic arteries which by stretching and

contracting assisted in the forward movement of the blood. The young patients thus showed an ability to adjust their circulatory mechanism to the heart block more simply than the others and without imposing the added strain which the compensatory systolic hypertension exerts upon the cardiovascular apparatus.

In the 3 cases in which high blood pressure existed the increase was evident only in the systolic pressure. This type of hypertension, then, is the direct result of increased ventricular discharge and bears no relation to the peripheral resistance except insofar as the high pressure depends upon the elasticity of the arterial system. Such hypertension is occasionally seen in persons with senile arteriosclerosis without heart block, but is fundamentally different in its nature from primary or essential hypertension. In the latter condition the fault lies in an increased peripheral resistance without an increase of the stroke volume and cardiac output, as has been shown by the authors[11] and others.

It is obviously impossible, therefore, to estimate from the arterial pressure alone whether the cardiac output per beat or per minute is normal. On the one hand, the blood pressure may be normal, with a marked increase in ventricular discharge, as in the first 2 cases of this series; on the other hand, the arterial pressure may be markedly elevated, although the cardiac output is not increased, as in cases of essential hypertension.

Venous Pressure. The venous pressure was normal in the 4 patients who were compensated at rest. The fifth case had an elevated venous pressure and also showed evidence of marked peripheral venous congestion. It is evident, therefore, that heart block *per se* does not tend to increase the venous pressure above the normal limits.

Vital Capacity. The vital capacity of the first case was normal. The reason for the somewhat lowered vital capacity in the second case is not evident, since she showed no objective or subjective evidence of pulmonary disease or venous stasis. The diminished vital capacity in Cases III and IV is in accord with the usual findings in persons who show a lowered cardiac reserve of similar extent.

Cardiac Output and Velocity of Blood Flow. Several workers have concluded, as a result of clinical observations and assumptions, in particular by taking the high pulse pressure as an index of increased ventricular discharge, that the output per beat in heart block is greatly increased. Von Bergmann and Plesch,[12] in 1909, applying the Fick principle, computed the cardiac output per beat and per minute in 1 patient and found the stroke volume increased to 200 cc. Lundsgaard,[13] Liljestrand and Zander[14] and most recently Smith, Walker and Alt,[15] using the Field and Bock application of the Fick principle, estimated the cardiac minute volume to be essentially normal during rest, with a consequent increase in the output per beat. During exercise patients with total block differ in their

ability to increase the cardiac output normally.[13,14,16] It is evident that this ability depends to a certain extent upon whether or not the ventricular rate is increased by exertion, since of all the cases reported only those who responded to exercise by a considerable increase in ventricular rate showed a normal increase in cardiac output.

The cardiac outputs of Cases I to IV in our series were determined. The technical procedure could not be carried out on Case V because of the pulmonary congestion. The cardiac outputs per minute as estimated in the 4 cases fell within the normal range. (Tables I and II.) Although the total cardiac outputs per minute were somewhat below the normal average, the blood flows per 100 cc. of oxygen consumption agreed closely with the average normal figure. To maintain this normal minute volume output of the heart in the presence of a markedly lowered heart rate the systolic discharge per beat had to be increased to a considerable extent in these patients. Our findings, therefore, agree closely with those of other observers as to the increase in stroke volume output and the maintenance of an essentially normal minute volume output at rest. No direct estimations of the amount of increase in blood flow during exercise were made.

The circulation rate from arm to face was determined in Cases I, II and IV. Changes in the circulation rate and in the cardiac output usually run parallel. However, if the cross section of the vascular bed is increased, the circulation rate may be greatly diminished without change in the cardiac output. In Cases I and II the circulation rate was normal. In Case IV, in spite of a normal cardiac output, the circulation time was greatly prolonged. Since the circulating blood volume in this patient was not increased, it would seem that there was a relative increase in the proportion of blood in the lungs with an increase in the cross sectional extent of the pulmonary vascular bed. That this increased blood volume in the pulmonary circuit does not invalidate the procedure for the determination of the cardiac output is evident from the fact that her arterial blood saturation was normal (90 per cent) and her alveolar carbon dioxid tension was within normal limits.

Peripheral Blood Flow. To check our findings as to cardiac output further and to gain some idea of the tissue consumption of oxygen, the oxygen and carbon dioxid contents and the arteriovenous oxygen and carbon dioxid differences of blood drawn from the cubital and femoral veins were measured. Although changes in the arteriovenous oxygen and carbon dioxid differences do not necessarily run parallel to changes in the cardiac output or blood flow as a whole, nevertheless, in our experience, a rough parallelism does exist—since the vessels from which the blood is drawn drain skeletal musculature (in particular, the legs) which represents at least 30 per cent of the oxygen consuming tissues of the body. Normally there is considerable individual variation between the

arteriovenous oxygen and carbon dioxid differences, but such variations fall within a definite range. Arteriovenous differences markedly higher than this range, therefore, are a strong indication of a reduction in the total blood flow. Our findings tend to corroborate this theory. (Table III.) In Cases I and IV, in which normal cardiac outputs were determined by the Fick principle, the arteriovenous oxygen and carbon dioxid differences from both arm and leg fell well within the normal range. In Cases I to IV the difference in carbon dioxid tension between alveolar and virtual venous gas samples was within the normal range (Table I)—a further indication of normal tissue exchange of gases. In Case V, who clinically was decompensated at rest and on whom it was technically impossible to determine the cardiac output, the arteriovenous oxygen and carbon dioxid differences were found to be definitely higher than the normal range. This suggests that in this patient the blood flow was diminished. Such diminished cardiac output in the presence of circulatory failure is to be expected, as it was also found by the authors in a group of patients with rheumatic heart disease.[17]

No evidence of an increase in the blood flow through the legs of Case V was found in spite of the fact that there was marked edema of the lower extremities. This is contrary to the finding reported by Harrison and Pilcher[18] of a decreased oxygen utilization from the blood flowing through an edematous extremity.

Lactic Acid and Arteriovenous Oxygen Difference at Rest and After Exercise. To throw further light on the state of the peripheral circulation both at rest and following mild exercise, lactic acid and arteriovenous oxygen difference determinations were made on Case I (L. S.) at rest and at intervals after he had performed a mild exercise (climbing two flights of stairs at a slow rate). In Table IV these values are given with the corresponding normal ranges and normal averages from identical procedures on a series of 10 healthy persons. It will be seen that the changes in arteriovenous oxygen difference were similar to the normal in direction and degree both in the arm and leg. Following exercise the patient's heart rate rose momentarily to 70, remaining regular, but subsided within thirty seconds to the resting level of 40.

The lactic acid content of the blood is also given in Table IV and Chart I, where it is compared both with the normal findings and those obtained in 10 compensated patients with heart disease. It will be seen that following exercise the rise is somewhat less than in the average normal case, and markedly less than in cardiac patients.[19] Since this man was a trained athlete, this finding, which is in accord with the work of Dill, Talbott and Edwards[20] on the effect of training on the circulatory mechanism, indicates that even in the presence of heart block the peripheral circulatory responses may be normal.

The Hemoglobin Content of the Blood. As judged either by the hematocrit readings or the oxygen capacity, none of the patients showed evidence of an increase in the amount of circulating hemoglobin, that is, a polycythemia. (Table I.) Case III showed evidence of a moderate anemia, such as occasionally occurs with advanced arteriosclerosis.

TABLE IV.—ARTERIOVENOUS OXYGEN DIFFERENCE AND LACTIC ACID CONTENT OF BLOOD TAKEN AT REST AND AT INTERVALS FOLLOWING EXERCISE IN CASE I.

Case.	Arteriovenous oxygen difference, vol. per cent.				Lactic acid, mg.				
	Resting	After exercise.			Resting	After exercise.			
		30 sec.	10 min.	20 min.		30 sec.	10 min.	20 min.	40 min.
LEG:									
I (L. S.)	6 9	14 6	3 9	7 3	15 6	18 8	16 4	..	16 4
Normal average	3 3	10 0	3 3	4 1	12 2	27 5	18 4	17 0	14 5
Normal range	1 to 8	7 to 13	1 5 to 5	2 5 to 7 5	8 8 to 15 1	17 4 to 43 8	15 3 to 26 9	14 4 to 22 6	10 8 to 17 5
ARM:									
I (L. S.)	4 3	10 5	4 5	...	13 3	16 8	15 4		
Normal average	3 6	9 8	3 8	...	13 5	16 0	15 8		
Normal range	1 to 5	4 to 12	1 to 5	...	9 8 to 17 2	13 1 to 20 7	13 to 18		

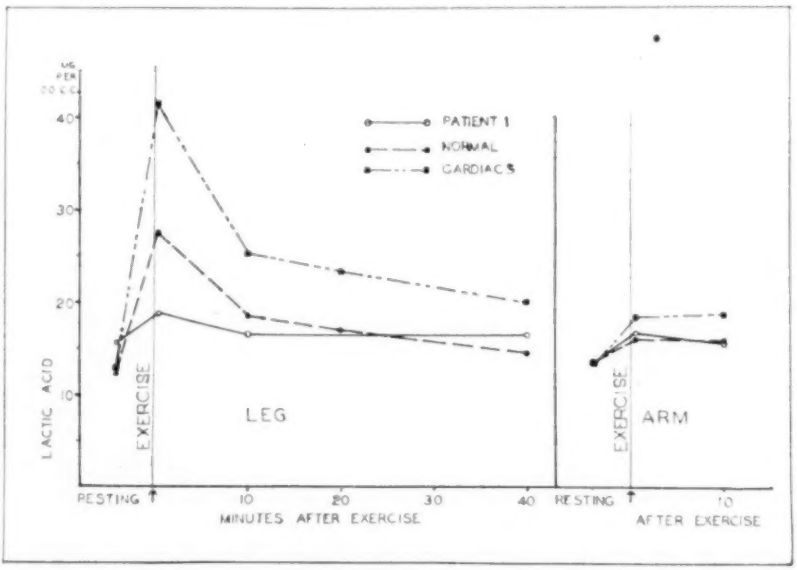

CHART I.—Lactic acid content in blood from arm and leg of Case I (L. S.), resting and at intervals after a stated exercise, compared with average values of a series of normal persons and of patients with heart disease.

Blood Volume. In each of the 4 patients in whom the blood volume was determined a reduction in the amount of circulating blood was found. (Table I.) Since this reduction in circulating blood volume existed without a decrease in the blood pressure or an increase in the minute volume flow, it is evident that there must have been a decrease in the extent of the peripheral vascular bed. In view of the fact that there was in no case any evidence of markedly increased peripheral resistance, it is most unlikely that the reduction took place to any extent in the arteriolar or capillary systems which are chiefly responsible for peripheral resistance.

Basal Metabolic Rate. In every case the basal metabolism was below the theoretical normal, although in only 1 case (Case I) did it fall below the lower limit of normal, namely, −15. (Table I.) It is not clear whether the organism readjusted itself to the altered circulatory conditions by decreasing its oxygen consumption or whether some underlying physiologic condition produced both complete block and a lowered metabolism.

Discussion. As a result of these observations on 5 cases of total heart block it is possible to summarize the circulatory changes which occurred in these patients. The blood flow was essentially normal at rest so long as the patient did not show evidence of circulatory failure in bed. To maintain a normal blood flow with a greatly reduced heart rate it is necessary for the output of the heart per beat to be increased markedly, and secondarily for the systolic arterial pressure to be raised, provided the peripheral vascular system is sclerosed and rigid. The circulating blood volume in the patients was somewhat reduced, and there was probably a diminution in the extent of the peripheral vascular bed. The peripheral resistance, however, was not increased. Whether our findings of a somewhat lowered basal metabolism has any relation to the heart block—either as cause or effect, it is impossible to state.

The symptoms of patients with heart block are of two types: (1) those of congestive or anginal heart failure, resulting from the myocardial degeneration which often accompanies the condition, and of which the heart block may be merely one manifestation; (2) the Adams-Stokes attacks, which are probably due to insufficient cerebral circulation brought about either by the inability of the heart to respond to the demands of exertion, by alterations in the peripheral circulatory adjustment, or, and this is probably the most common cause, by a local decrease in the irritability and responsiveness of the ventricles with periods of ventricular asystole. It is evident that complete heart block is not incompatible with a normal life and that the prognosis as to health and life is much more dependent on the presence or absence of accompanying myocardial disease than on the block itself.

Summary and Conclusions. 1. Studies were made on 5 patients with complete heart block, 2 of whom showed no, 2 moderate and 1 pronounced functional disability.

2. The 2 patients with no functional incapacity and no arteriosclerosis had normal arterial blood pressures. The remaining 3 had a systolic hypertension.

3. In the absence of cardiac failure the venous pressure was normal.

4. In the 4 patients with no circulatory failure at rest normal values for the cardiac outputs per minute were found. The cardiac outputs per beat in these patients were increased 40 to 50 per cent above the normal. In the fifth patient, with circulatory failure in bed, indirect evidence of a decreased blood flow was obtained.

5. The circulating blood volume was reduced in each of 4 patients. It was not measured in the fifth.

6. Four patients had basal metabolic rates in the lower part of the normal range; the fifth had a metabolism 20 per cent below normal.

7. The degree of elevation of the lactic acid and the changes of blood gases following exercise were normal in 1 patient who had good functional capacity.

8. The increased stroke volume of the heart, the systolic hypertension, the reduced blood volume and possibly the somewhat lowered basal metabolic rate may be considered compensatory responses tending to maintain a constant and adequate blood supply to the tissues during the prolonged diastolic pauses consequent upon the slow heart rate.

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AORTIC ANEURYSM RUPTURING INTO THE CONUS ARTERIOSUS OF THE RIGHT VENTRICLE.

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In a recent study of 100 aortic aneurysms coming to autopsy[1] it was noted that rupture occurred in 47 per cent of the cases. In the large majority of these the site of rupture was either into the pleural cavities or into some portion of the bronchial tree; rarely rupture occurred into one of the great vessels of the mediastinum, there being 2 cases in which an arteriovenous aneurysm was formed by perforation of the aneurysm into the superior vena cava. In 1 case the aneurysm had exerted sufficient pressure upon the pulmonary artery to cause some erosion of the vessel and to have been the immediate cause of death. In the case herewith reported rupture occurred into the conus arteriosus of the right ventricle. Antemortem diagnosis of the aneurysm was not made. The resulting physical signs were so typical of interventricular septal defect that the clinical diagnosis of Maladie de Roger was made, along with that of syphilitic aortitis and aortic insufficiency.

Case Report. *History.* H. C., a negro man, aged 28 years, laborer by occupation, was admitted to the John Sealy Hospital, October 2, 1929, complaining of shortness of breath and pain in the left chest. He dated his illness as beginning 3 months prior to entry, at which time he first noticed sharp and shooting pains about the heart and a feeling of fullness in the left chest. The pain was paroxysmal in nature, substernal in location and of short duration. About 2 months later he developed rather suddenly a severe moderately productive cough associated with severe dyspnea. Occasionally the sputum would be blood tinged. The dyspnea increased rapidly, and for the past week he was compelled to spend the entire night in a sitting posture in order to breathe. Night sweats had been experienced for about a week. There had been a loss in weight of 18 pounds.

The family history was irrelevant. With the exception of a penile sore at the age of 22 years, his past history was devoid of serious or significant illness.

Physical Examination. The patient was well developed, well nourished and showed marked respiratory distress. There was noticeable pulsation of the great vessels of the neck. Slight cyanosis was present. Many moist râles of the crepitant variety were heard over the bases of the lungs. The pulse was regular, rate 110 and Corrigan in character. Visible pulsation of the peripheral vessels was noted. Capillary pulsation was observed in the nail bed. The blood pressure in both arms was the same, 120 mm. Hg systolic and 10 mm. Hg diastolic.

The heart was greatly enlarged, the left border being 12 cm. from the midsternal line in the sixth left intercostal space. The supracardiac dullness measured 7 cm. A pronounced superficial systolic thrill was felt over the precordium, maximal in the third and fourth interspaces adjacent to the left border of the sternum. On auscultation over the aortic area a short systolic murmur was heard, followed by a long, loud blowing, diastolic murmur which was transmitted downward along the left border of the sternum toward the apex of the heart. Maximal, in the fourth left intercostal space there was heard an intense, superficial, rasping systolic murmur, which was transmitted well over the entire precordium. At this same area a diastolic murmur was heard. However, it was thought to have been generated at the aortic area. No edema was present.

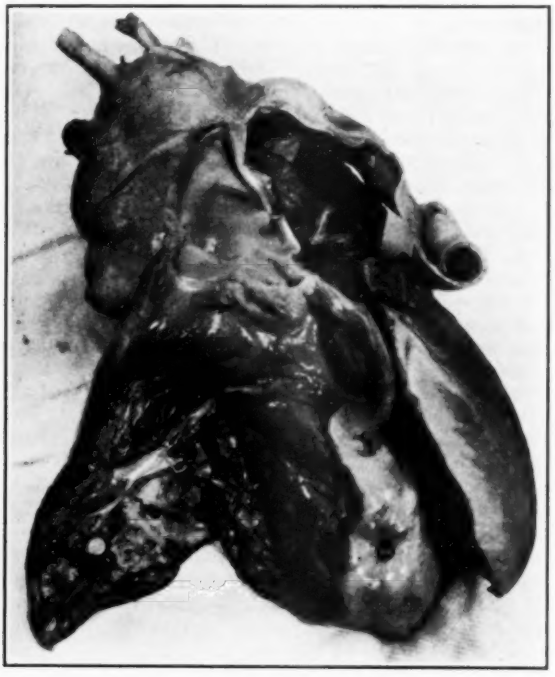
A daily elevation of temperature occurred, usually reaching 100° F. The leukocyte count was 14,200, with 74 per cent polymorphonuclear forms. The blood culture was negative. A teleoroentgenogram revealed the transverse inside diameter of the chest 28 cm., transverse diameter of heart at apex 17 cm. and aortic arch 7 cm. Fluoroscopic study of the heart and great vessels was not done. The electrocardiogram showed a moderate degree of right axis deviation and a sinus tachycardia. The Wassermann reaction on the blood was 4+.

Course in Hospital. In spite of rest in bed, digitalization and the other usual therapeutic measures, there was a progressive increase in the degree of cardiac failure. Edema of the lower extremities appeared along with an accumulation of fluid in the abdominal cavity and the right chest. Death due to cardiac failure occurred 15 days after admission.

The clinical diagnosis was congenital heart disease, with interventricular septal defect, syphilitic aortitis with extensive destruction of the aortic valves and possibly a subacute bacterial endocarditis.

Necropsy. The heart was about twice the normal size and showed rather marked dilatation of all chambers. The wall of the left ventricle was 1.5 cm. in thickness. The ascending portion and the arch of the aorta was the seat of a diffuse saccular dilatation which measured 10 cm. in its greatest diameter. The innominate and left common carotid arteries arose from the dome of the sac. A large mixed thrombus nearly entirely filled the sac.

Behind the right posterior cusp of the aortic valve the sinus of Valsalva was pouched out to form a small aneurysmal sac which extended down just posterior to the orifice of the pulmonary artery. The bottom of this sac opened into the cavity of the right ventricle through an aperture 1 cm. in diameter, which passed through the lower part of the posterior leaflet of the pulmonary valve. This leaflet was fairly adherent to the wall of the pulmonary artery at its base. The edges of the aperture were rounded and smooth, and it appeared to have been present for some time. There were no clots in this aneurysmal sac, which made it evident that blood passed freely from the aorta into the right ventricle during life. The aortic ring showed considerable dilatation. The aortic valves showed some thickening and rolling of the free edges. In the intima of the ascending portion of the aorta were found multiple linear and stellate scars. (See illustration.)



View from right ventricle, showing the conus arteriosus and the pulmonary valves. The perforation is seen in the lower portion of the posterior valve. (See arrow.)

The anatomic diagnoses were hypertrophy and dilatation of the heart, syphilitic aortitis and aortic valvulitis, aneurysm of the ascending portion and the arch of the aorta, aneurysm of the right posterior sinus of Valsalva with rupture into the right ventricle.

Comment. Aside from the chest pain, which was thought to be a result of the syphilitic aortitis, there was nothing in the history or physical examination to suggest the presence of an aneurysm. It was not visualized on the flat Roentgen ray plate because of the

fact that it extended in an anteroposterior direction. Fluoroscopy, had it been done, would have undoubtedly made the diagnosis because of the obliteration of the posterior mediastinal space.

Discussion. Rupture of a congenital aneurysm of one of the sinuses of Valsalva, usually the right, into the right ventricle has been reported several times. Abbott[2] reported a case and collected 7 others from the literature. An additional case, not included in Abbott's review of the literature, is reported by Gage.[3] The majority of these cases were associated with defects in the interventricular septum. Rupture of an acquired aneurysm into the right ventricle, however, is a much rarer condition, only 2 cases being found in the literature after a rather careful search.

Laycock,[4] in 1860, reported a case occurring in a man, aged 56 years, whose symptoms had been present for 4 months. There was marked cardiac enlargement, a visible aneurysm in the neck and a distinct thrill over the precordium which was associated with a loud, rasping, double murmur heard loudest over the aortic area. Death was due to progressive cardiac failure. At necropsy the entire aorta was found to be the seat of extensive disease, which, apparently from the description, was syphilitic in nature. A large fusiform aneurysm of the ascending aorta was present, from which a smaller sac had budded off and ruptured into the conus arteriosus of the right ventricle.

The other case was reported by Lichtenburg,[5] in 1865. It occurred in a young man, aged 29 years, who had been in apparent good health. The outstanding symptom was severe palpitation. A thrill over the lower region of the heart was present, and "each sound was replaced by a strong bruit." Death occurred 14 days after the onset of symptoms from heart failure. Postmortem examination revealed a "rounded aperture the size of a goose quill behind the posterior semilunar valve which opened into a sac the size of a filbert." The aneurysmal sac bulged into the right auriculoventricular opening and at one point had ruptured. From the description of the aortic valves and also the liver, syphilis seemed a likely etiologic factor.

The physical signs resulting from this abnormal communication between the two circulations are essentially the same as those described by Scott[6] where the aneurysm had ruptured into the pulmonary artery. An intense, superficial thrill was present in all cases. In the 2 previously reported cases the resulting murmur was continuous in character. In the case reported here the character of the murmur was somewhat obscured by the associated aortic insufficiency. The sudden establishment of the arterial venous shunt results in such marked disturbance of cardiac function that congestive heart failure appears rapidly and is the cause of an early fatal termination. In all cases syphilis was the etiologic factor in the production of the aneurysm.

Summary. A case of acquired aneurysm of the ascending aorta with rupture into the conus arteriosus of the right ventricle is reported. The resulting physical signs simulate very closely those of congenital heart disease. The 2 previously reported cases are briefly reviewed.

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A CASE OF CONGENITAL STENOSIS OF THE PULMONARY VALVE, WITH LATE ONSET OF CYANOSIS: DEATH FROM CARCINOMA OF THE PANCREAS.*

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Our knowledge of the classification and physiology of the congenital cardiac anomalies has advanced remarkably during recent years, thanks to the excellent work of Abbott, Lundsgaard and others. One group of congenital cardiac cases which is of particular interest is that in which the cyanosis first makes its appearance some years after birth. We wish to report such a case that presents other points of unusual interest, among them being the fact that the cyanosis was not due to oxygen unsaturation of the arterial blood, and was limited to certain areas, thus giving the patient a striking and bizarre appearance.

* Read before the Section on General Medicine, College of Physicians, May 26, 1930.

Case Report. The patient was born in Scotland of healthy ancestry and was not a "blue baby." There was nothing in his early life to indicate that he was abnormal. He was unusually athletic and a devotee of "soccer" and cross-country running. He saw 4 years of active service during the World War, and was known in his company as an excellent boxer, sometimes competing two or three times on the same night. Both during and after the war he underwent several thorough examinations, but was never led to believe that there was anything abnormal about his heart or his color. He came to America, in 1924, worked as a truck driver and was required daily to lift numerous heavy milk cans onto his truck. Dr. Robert L. Gray informs us that he examined the patient for insurance in 1925 and in 1928, and that on neither occasion did he note anything abnormal about the patient's heart or his color.

The patient stated that for 2 months prior to coming under our observation he had noticed swelling of the ankles at night and that he had more recently suffered from dyspnea. He was seen during 2 dyspneic attacks by Dr. Gray, who noted the usual signs of acute cardiac decompensation, together with a remarkable blue color of the skin. The patient was thereupon advised to enter the Episcopal Hospital, where he was first seen by us, in April, 1929. The blue color had first been noticed 2 years before, following an ocean bath at Atlantic City. At this time it wore off promptly, but returned whenever he was chilled or when walking against the wind, and in recent months it was noted continuously, though in varying degrees. He had never had sore throats, rheumatic fever nor chorea. He was not subject to colds during the winter and had never before had a serious illness. He was very temperate in his habits, using no tobacco and little alcohol. Because of his cyanosis, he was closely questioned regarding exposure to drugs, but we were unable to elicit a history of contact with or ingestion of any toxic chemicals or drugs.

Examination revealed a very well-developed and well-nourished young man, aged 32 years, lying quietly in bed without dyspnea, but with a remarkable bluish-purple tinge of the skin. The color was deepest in the face, where it was a splotchy purple, especially at the tip of the nose, the cheeks and the lobes of the ears. Looking more closely, it might be seen that this color was mainly or entirely due to the presence of engorged, deeply purple superficial bloodvessels, many of which were visible to the naked eye as loops or dots lying just beneath the surface of the skin. Microscopic examination of the finger by the Lombard method showed capillaries which were more numerous and more tortuous than one usually finds in normal subjects, some capillaries having as many as four loops visible. Portions of the trunk and extremities also presented a purplish appearance, but not to such a degree as the face. On stroking the skin, the finger left a blanched trail for a few seconds, this quickly gave way to a bluish discoloration, and this, in turn, was followed by a brick red color with blanched margins, the latter phenomenon lasting about 5 minutes. There was absence of cyanosis of the lips and finger-nail beds. The mucous membranes of the mouth were somewhat injected but not cyanotic, and the tonsils were small. The cardiac measurements as shown by a teleroentgenogram (Fig. 1) were: M. L., 10 cm.; M. R., 4 cm.; length, 16.3 cm.; arch of aorta, 5.5 cm.

Dr. Bromer, in commenting upon the appearance of the Roentgen ray, reported: "The 6-foot film shows slight increase in the width of the left ventricle shadow, also in the right auricle shadow. The appearance is more characteristic of mitral regurgitation than of pulmonary stenosis. There is no marked cardiac dilatation or hypertrophy present." Over the entire precordium there was a very harsh systolic murmur which was best heard at the third interspace to the left of the sternum, and was transmitted into the left axilla and to the left scapular angle. There was little or no

transmission to the vessels of the neck. No thrill was noted by us either while the patient was at rest or during exercise, but Dr. James Kay on one examination noted the presence of a systolic thrill near the apex after exercise. The pulse and respiratory rates respectively with the patient at rest were 88 and 18. After exercise his pulse rose to 112, the respirations to 22, but within 2 minutes his pulse fell to 88 and respirations to 20. The arterial blood pressure was 102 systolic and 68 diastolic. The venous pressure was not measured but no venous pulsation was present, and the veins of the hand were seen to collapse when the hand was raised to the level of the chin. The tourniquet test of capillary resistance (Rumple-Leede's phenomenon) was negative. The spleen was not palpable, the liver was felt about 3 cm. below the costal margin and was hard. The lungs were normal. Although the toes were a little clubbed, the fingers showed no clubbing. There was some edema of the ankles. The eyegrounds were reported by Dr. Fewell as normal in appearance. Blood counts were as follows:

Date, 1929.	R. B. C., millions.	W. B. C., thousands.	Polymorphonuclear neutrophils, per cent.	Hemoglobin per cent, (Dare).
April 26	4.5	6.4	73	70
May 10	5.0	11.5	68	85
May 13	5.0	11.0	71	80
Oct. 30	4.6	9.9	73	98

The urine was negative except for a faint trace of albumin. The Wassermann reaction of the blood was negative. The blood urea nitrogen was 33 mg. per cent, the plasma CO_2 was 40 and the fasting blood sugar 0.05 per cent. A glucose tolerance test showed some disturbance in the glycolytic function for 2 hours after the ingestion of the glucose solution, the blood sugar was 0.26 per cent and there was 1.1 per cent of sugar in the urine. The electrocardiogram showed right ventricular preponderance but was otherwise normal. (Fig. 3.) The vital capacity of the lungs was 3900 cc. (5 per cent below the expectation for one of his age, height and weight). The response of the skin of the forearm to needle pricks through solutions of adrenalin and also histamin was normal.

Thinking that perhaps a communication might exist between the right and left cardiac chambers, which, under conditions of increased pulmonary pressure, would allow the entrance of venous blood into the arterial circulation, a test was devised which it was thought would artificially increase the pressure within the right cardiac chambers. The patient was instructed to inhale, and while attempting forced exhalation through a mouthpiece ending in a mercury manometer, the skin of the body was scrutinized for any evidence of increase in the cyanosis. Several prolonged efforts at exhalation, registering pressures of 20 to 50 mm. of mercury, failed to produce any noticeable deepening of cyanosis, and it was concluded that this was evidence against the presence of a communication between the right and left cardiac chambers of sufficient size to be of physiologic importance.

Course. On rest and digitalis therapy the edema of his ankles disappeared and about 1 month after admission he asked for his discharge. Two days before leaving the hospital, however, he developed diarrhea.

Late in the summer we both had the opportunity of seeing him at his home, and learned that the diarrhea had never ceased, there being eight to ten watery bowel movements a day, though he never passed any blood. He had lost a great deal of weight, was quite weak and had curious seizures of shortness of breath, choking cough and at times irrational periods in which he went over some of the events of his life in the army, frequently giving military commands to imaginary forces. These cerebral

attacks at times lasted all night, leaving him rational in the morning, without any memory of their occurrence. The liver had become more enlarged, its edge being at the level of the umbilicus; it presented a smooth surface under the palpating hand. The skin of the legs was tense and shiny. Some weeks later he developed weakness of the left leg, with exaggeration of the patellar reflexes and bilateral ankle clonus and Babinski reflexes. Three days before death he was readmitted to the hospital, aphasic, a little agitated, in a semidelirious state. Dr. George Wilson made the following note on November 1, 1929: "Bilaterally increased reflexes; Babinski, ankle and patellar clonus. Myoclonic twitchings of both hands and the right side of the face suggestive of cortical irritation. He attempts to obey simple commands but is speechless. The neck is stiff. The presence of bilateral signs with muscular twitchings, the predominance of motor weakness in the lower extremities and the cerebral disturbances point to a thrombosis of the longitudinal sinus."

The patient died on November 3, 1929, and an autopsy was performed on the same day by Dr. John Klopp.

Autopsy. Only the significant findings will be reported. On opening the chest the right side of the heart seemed dilated. The organ weighed 205 gm. and measured 13 by 9 by 4 cm. The epicardium was pale and glistening. There was a slight excess of subepicardial fat. The right ventricle measured 6.5 by 9 cm. and the left 4 by 9 cm. The sizes of the various orifices were as follows: Mitral, 8.5 cm.; tricuspid, 9 cm.; aortic, 6.4 cm.; pulmonary, 3.5 cm. The endocardium presented a normal appearance and no evidence of valvulitis was present. No interventricular septal defect was found. A probe could be passed through the foramen ovale, but the latter was guarded on both sides by large folds making it, in the opinion of those who saw it, anatomically patent but functionally closed,* so that in the opinion of the pathologist there was no functional communication during life between the auricles. The wall of the left ventricle was 1.4 cm. thick and that of the right 0.6 cm. Both auricular walls measured 14 mm. The heart muscle was dark red, and histologically showed hypertrophy and edema. There were a few yellow plaques in the aorta. The pathologic diagnosis was congenital pulmonary stenosis, hypertrophy and dilatation of the heart.

The pancreas measured 12 by 4 by 3 cm., was of a yellowish color, firm consistency and contained several nodules in its head which macroscopically suggested neoplasm and microscopically proved to be adenocarcinoma.

The liver weighed 2200 gm. The surface was smooth and the edge sharp. It was studded throughout with yellow umbilicated circumscribed lesions of metastatic adenocarcinoma. The lymph nodes about the cystic duct showed carcinomatous infiltration but had not obstructed the flow of bile from the gall bladder. There was a mass of retroperitoneal lymph nodes infiltrated with carcinoma. Evidences of metastasis within the lungs were carefully sought for, but not found.

The brain failed to show any lesion except axonal chromatolysis and ischemic cell disease. The longitudinal sinus was not thrombosed.

The *histologic* examination of the specimen of the skin showed some thinning of the superficial layers and an increase in the amount of loose fibrous tissue present. There was an increase in the number of bloodvessels, the walls of the latter being greatly thickened. (Fig. 2.)

Discussion. In spite of the late onset of cardiac symptoms, it is hard to conceive that the pulmonary stenosis could have been other

* A slitlike opening in the fossa ovalis has been found to be present in somewhat over 30 per cent of adult hearts. (Piersol.)

than a congenital anomaly. No pathologic evidence of an inflammatory process either recent or remote was found, nor did the history point toward rheumatic fever or any illness which might lead to a valvular lesion. While other writers have reported cases of congenital pulmonary stenosis which lived longer or developed cyanosis later in life than our patient, we know of no instance where the victim of this cardiac anomaly showed special athletic prowess; on the contrary, most cases have been found to adopt a sedentary mode of life. Death from carcinoma is also an unusual finding, the commonest causes of death in congenital pulmonary stenosis being pulmonary tuberculosis and bacterial endocarditis.

The cyanosis in this case differed in appearance and distribution from that caused by cardiac decompensation. It was not due to oxygen unsaturation of the arterial blood, for, as has been said, the finger-nail beds and lips were not cyanotic; furthermore, Dr. Leon Collins found that in a sample of blood from the radial artery the oxygen saturation was normal (oxygen content, 17.6 volumes per cent; oxygen capacity, 18.6 volumes per cent; the oxygen saturation, therefore, 94.6 per cent).

In contradistinction to that ordinarily seen in cardiac decompensation, the cyanosis in our case was limited to certain localities of the skin. Local cyanosis is seen normally as a result of exposure to cold, and pathologically in a number of conditions, including erythromelalgia and Raynaud's disease. It is due to increased oxygen consumption in the capillary bed due to venous stasis (Lundsgaard's D factor), thus rendering the blood within the capillaries similar to venous blood as regards color and oxygen content. The cause of the venous stasis in Raynaud's disease, according to Lewis, who has recently made an exhaustive study of the subject, is arterial spasm. Where the fingers are involved by cyanosis in their entire length, he asserts that the vessels implicated are the digital arteries in their entire length. In our case the stasis was caused, or at least accompanied by a dilatation of the superficial vessels of certain areas of the skin, notably the nose, cheeks and portions of the anterior aspect of the trunk, and to a lesser extent the upper extremities.

Morgagni was the first to recognize the fact that certain cases of congenital heart disease owed their color to dilatation of the skin vessels, and cases of congenital heart disease have been reported by Carpenter and others, where not only the skin but also the internal viscera partook of such vascular dilatation. Vascular dilatation was carefully sought for in sections of the visceral organs removed at autopsy, but was not found in our case. Just what the relationship of dilated bloodvessels and congenital heart disease may be is a matter for speculation. We feel, however, that the fact that this combination has been described previously renders it unlikely that it is merely coincidence either in our own case or in the others reported in the literature.

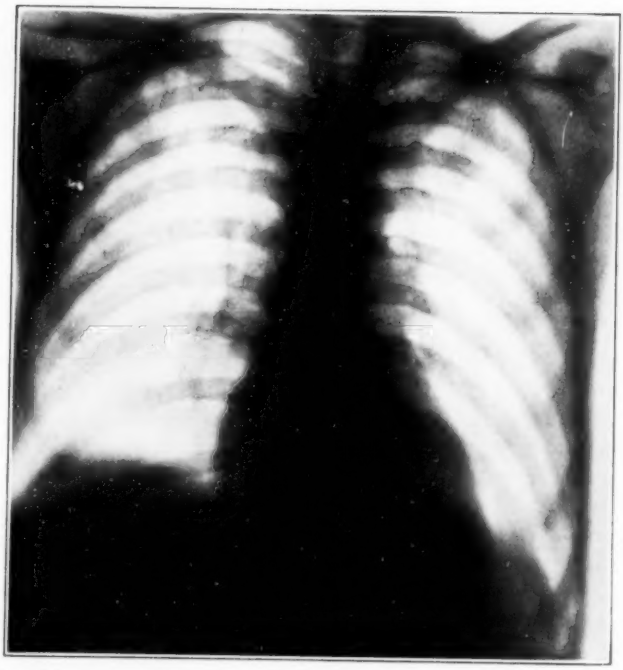

FIG. 1.—Teleroentgenogram of a case of congenital stenosis of the pulmonary valve, showing slight increase in the width of the right auricular and left ventricular shadows. Prominence of the pulmonary arc, usually found in cases of congenital pulmonary stenosis, is absent in this case.

FIG. 2.—Section of skin (magnified × 80), showing numerous bloodvessels with thickened walls. The localized cyanosis in this case was presumably due to the presence of numerous dilated superficial bloodvessels in certain localities.

FIG. 3.—Electrocardiogram, showing the right axis deviation usually present in congenital pulmonary stenosis. (Chief ventricular deflections intensified with India ink for clearer reproduction.)

Summary. The case of a patient with simple congenital pulmonary stenosis is presented, who after an exceptionally athletic career gradually developed localized areas of cyanosis believed to be due to the stasis of blood within dilated minute bloodvessels of the skin. Attention is called to the fact that cyanosis due to vascular stasis is not uncommon in congenital cardiac disease, and occurs in other conditions as well. Death in this case came at age 33 as a result of carcinoma of the pancreas, an unusual complication of congenital pulmonary stenosis.

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POSTURAL HYPOTENSION: A CASE REPORT.*

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With the recent case of Riecker and Upjohn,[1] 8 cases of marked postural hypotension have been reported: 3 by Bradbury and Eggleston,[2] in 1925, 2 by Ghrist and Brown,[3] in 1928, and 2 by Vaughan[4], in 1928. Another case of marked postural hypotension with the characteristic syndrome is here presented.

In this case, as in the previous cases, the symptoms of anemia of the brain came regularly with the upright position and promptly disappeared with the lowering of the head to the body level, these phenomena recurring quite constantly over a period of years.

Case Report. The patient, a successful attorney, aged 34 years, came under observation in September, 1930, complaining of dizziness, faintness and mental haziness, that came on when he continued in an upright position for any extended period, of chronic edema of the feet and legs below the knees and of chronic diarrhea, with two or three watery stools a day.

The observation period ended on October 11. The following notes are from the case records: He states that he was very active and enjoyed good health in childhood and in youth until he was 21 years of age. During the fall and winter of 1917–1918 he was exposed to cold and hardships. He developed a severe cough and became generally run down, though he continued at rather exacting and exhausting duties. In April, 1918, while already in a weakened and much fatigued condition, he attempted to tramp some 9 miles, carrying a heavy load on his back. Near the end of this

* Published with the permission of the Medical Director of the U. S. Veterans Bureau.

journey it became necessary for him to run for some distance up a small hill. As he ran he suddenly had the sensation as if something had broken loose low down in his abdomen. He fell to the ground, but did not become entirely unconscious. After about 10 days' rest he felt much better and resumed his duties. However, to the patient's own mind, all his later physical troubles had their beginning when he felt that "something" break loose in his abdomen. Always after that he had a constant dragging sensation in the lower abdomen, and he never again regained his normal strength. During the following August he developed a severe diarrhea with abdominal cramps and frequent watery stools, but he still continued at his duties. One day, about this time, as he jumped from a truck to the ground he had a sudden feeling of extreme faintness and as if his abdominal organs were sinking down. At the same time he had pain and a queer feeling in the sacroiliac region and in the hips and legs. Though he was faint at this time, he did not lose consciousness. He had another and similar attack during October, 1918. In this attack, which also occurred as he jumped from a truck to the ground, he thinks that he actually lost consciousness for a few minutes. After that he had frequent periods of great faintness and dizziness whenever he continued for a long time in an upright position.

The diarrhea with watery stools continued from the summer of 1918 until 1922. Then, for 5 years, from 1922, to 1927, he was fairly free from the diarrhea; but in 1927 it returned, and most of the time since then he has had two to five watery stools each day. He has had no periods of constipation. He has not been subject to abdominal cramps in recent years, but he often has a "sinking sensation" in the abdomen. Associated with the evacuations of the watery stools, he frequently has a distress which he describes as deep in the abdomen, "in the sacroiliac region." He has never lived in the tropics, and he has never been told that any pathogenic intestinal parasites have been found in his feces, though his feces have often been examined for parasites.

His faintness and dizziness have been an increasing handicap during the years since 1918. However, he fitted himself for the profession of law, and for the past 5 years he has been quite successful in the practice of that profession, in spite of his handicap. For some years he has spent the greater part of his waking hours lying on a couch, in the prone position, with two or three cushions under his abdomen. In this position he carries on most of his professional work. He states that, with his body in this position, he can continue very exacting mental work for hours without fatigue. But his mind becomes fogged, his sight becomes blurred and his speech is stumbling after a period, maybe of only a few minutes, in a sitting or standing position. Walking or riding is even worse. However, immediately he lies down his thought, sight and speech becomes normal. In the courtroom he has found that he is at his best in very short cases or in cases where frequent recesses are granted, and that he is at a great disadvantage when he is forced to continue on his feet or in a chair. At such times, when he feels his mental faculties failing, he is apt to lose his self-control and, in attempt at self defense, is apt to resort to bitter and stinging words. He has often made further trouble for himself in this way. He has many times fallen in a semiconscious condition when he has forced himself to continue upright. On one occasion, in 1923, while working in his garden, he became faint and stumbled and seriously sprained or fractured his left foot. One evening, about 2 years ago, while walking the short distance from his office to his home, he became very tired and faint and fell, fracturing his right femur. However, it appears that at no time have these attacks been of a nature to raise the question of epilepsy.

Throughout these years the patient has noted that his pulse has been

slow, this more especially when he has been tired. He has also observed that with exertion or excitement his pulse has become slower rather than faster. He has noted, too, that his pulse has often been irregular and that this irregularity has been particularly apt to occur when he has been resting. A few years ago a physician gave him atropin medication for a short time. He felt rather better while on this treatment, but he states that he discontinued the atropin for the reason that he found his judgment was faulty while he was under its influence.

He gives no report of having had any definitely localized precordial distress, though for years he has been troubled with various chest pains, presumably of the nature of pleurisy. When very tired he has occasionally been troubled with a severe pain in the left forearm, wrist and palm. This pain has come "with startling suddenness and severity" and has, at time continued for as long as a half hour. At no time has this pain been associated with any chest pain. He has had no such pain in the right arm, wrist or hand.

For many years it has been the common observation of his family and his friends that he becomes very pale soon after he sits up or stands up and that his color becomes normal almost immediately with his lying down. He has observed for the past 8 or 10 years that his feet and legs have ordinarily been somewhat edematous and that they have become heavy and numb after walking a few blocks. He has not observed his hands or feet to be cyanotic or excessively damp or cold. He sleeps habitually with his face downward. He uses no pillow under his head, but he regularly sleeps with two or three pillows under his abdomen. He is not subject to night dyspnea, and ordinarily he has no nocturia.

The patient gives no report of having had rheumatic fever, chorea, scarlet fever or diphtheria and he emphatically denies all venereal infections. He gives no definite history of any serious respiratory disease during recent years. He was subject to occasional attacks of tonsillitis prior to tonsillectomy in 1921. He has used liquor very moderately and he smokes but two or three cigars a day. He denies ever having used drugs, and there is nothing in his records or in his personal appearance that is suggestive of drug addiction.

Family History. The patient's father and mother are both living and in fairly good health. He has 3 brothers and four sisters living and well. Two sisters died in childhood and 1 sister died in adult life, of cancer. The patient has been married since 1921. The wife is well. By this marriage she has had 2 early miscarriages and 4 children at term. The children are all normal and well.

Physical Examination. The patient is a slender, poorly developed and poorly nourished white man, 72½ inches tall and weiging 150 pounds, who had the appearance of his stated age of 34 years. His gait and movements are fairly active. He is evidently of an intellectual type and he seems to be mentally alert, but he has a melancholy expression of countenance. He sways notably when standing with eyes closed. He has a rounded upper dorsal stoop and slight lumbar lordosis; he seems to be unable to stand perfectly erect. The chest is of long type and is poorly developed, but symmetrical. The scapulæ are somewhat winged. The abdomen is long, flat and sagging. He has very slight tremors of the extended fingers. The fingers are not clubbed. The finger nails are quite normal. Flexion of the right hip is markedly limited. (History of fracture of neck of femur 2 years ago.) The patellar reflexes are active. The left foot is somewhat misshapen. (History of injury in 1923.)

When the patient is in the upright position his face, ears, neck and upper chest are ghastly pale and he has the appearance of one who is very ill or about to faint. However, when he lies down he immediately has a

perfectly healthy color. His skin is smooth, soft, normally moist and free from lesions. No gross scars of operations or injuries are noted. There is no cyanosis of the dependent hands or feet. The hands become quite white when they are elevated for a few moments. No varicosities are observed. Both legs below the knees are distinctly edematous and pit markedly with pressure.

His hair is thick, dark and glossy. His face is symmetrical. He wears glasses. He has no exophthalmos. His pupils are equal and regular and react to light, accommodation and convergence. The teeth and gums are well kept. The tongue appears normal. The breath has an extremely fetid odor. The thyroid appears normal and the superficial lymph nodes appear normal.

Summary of Further Observations. No definite evidences of disease were found in the upper respiratory tract. The physical and Roentgen ray findings of the lungs were essentially negative. The heart was found to be rather small and centrally placed. No precordial thrills were palpated. The cardiac sounds were somewhat muffled. No cardiac murmurs were heard. The rhythm varied with repeated examinations. At times the rhythm was perfectly regular; at other times marked sinus arrhythmia was observed; occasionally extrasystoles were noted. Repeated electrocardiograms gave no additional evidence except to show that the extrasystoles were ventricular in origin. The pulse rate was found as low as 40, though usually the range was 50 to 60 when the patient was lying down and 60 to 70 when he was sitting or standing. With the exercise of 100 hops the pulse rate of 48 (recumbent) was reduced to 45 (recumbent), and 2 minutes later the rate continued at 45. Firm pressure on the eyeballs caused no definite change in the pulse rate. Firm digital pressures, alternating on the right vagus and on the left vagus nerve in the neck, caused absolutely no change in the pulse rate. Later, the patient was given full doses of tincture of belladonna for a period of days. During this period the pulse tended to remain at the lowest rate rather than to increase.

The blood-pressure reading was 130 systolic and 74 diastolic with the patient in the sitting position and the arm hanging by his side. The arm was raised so that the elbow was at the level of the upper thorax and the blood-pressure reading was 110 systolic and 68 diastolic. The arm was then elevated so that the sphygmomanometer cuff was at the level of the head and the reading was 84 systolic and 60 diastolic.

With the patient standing, the abdomen was notably sagging in appearance. No abdominal masses were palpable and no abnormal tenderness was elicited by deep palpation. Firm pressure on the abdomen or a tight abdominal belt caused a lessening of the patient's dizziness.

Laboratory Data. Blood: Hemoglobin, 100 per cent; total red blood cells, 4,800,000 per c.mm.; total white cells, 8200; polymorphonuclears, 65; small mononuclears, 27; large mononuclears, 3; transitionals, 2; eosinophils, 2; basophils, 1. Blood sugar, 95 mg. Blood Wassermann reaction negative. Icterus index, 4. Van den Bergh test: Direct, negative; indirect, normal. Three basal metabolic estimates averaged −17, but the readings were not considered entirely satisfactory.

Gastric analysis was omitted because of the difficulty the patient experienced in attempting to take the tube. Ten sputum reports were negative. Urinalysis reports were normal. The feces were of liquid consistency. Traces of occult blood were reported. Endolimax nana and blastocystis hominis were found.

The Roentgen ray report of a gastrointestinal series, including barium enema, reads in part: "Haustra are poor in the transverse colon and practically absent in the descending colon and sigmoid. This is presumptive evidence of ulcerative colitis."

Comment. It is of special interest in the case of this young man with the characteristic syndrome of marked postural hypotension that his symptoms began on a definite date with a definite experience. It seems reasonable to assume that a lesion of the autonomic system was incurred at that particular time.

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THE LEUKOCYTIC REACTION IN TUBERCULOSIS OF INFANCY AND CHILDHOOD.*

Blood Studies With the Supravital Technique.

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The introduction of the cutaneous tuberculin test by Pirquet, in 1907, revealed the frequency of tuberculous infection in infancy and in childhood. A positive reaction, while more significant than in the adult, is not so readily appraised when considered in terms of the activity of the existing lesion. Of the laboratory aids available for evaluating more precisely the activity of tuberculous infection, the white blood count has of late been restored to a position of importance. It is the purpose of this paper to present a preliminary report, based on studies of the peripheral blood carried on during the past two years, in which the newer technique has been employed.

Although the white blood count has been related in the past with stages of resistance and activity in tuberculosis, it is only recently that it has been interpreted as reflecting the pathological state of the tuberculous lesion. This largely resulted from the added information acquired concerning the principal cell types involved in the tissues and organs in this disease. In 1925 Sabin and her

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coworkers,[1] on the basis of observations in experimental tuberculosis in rabbits, in which the supravital technique was used, concluded that the major effect of the tubercle bacillus was on the monocyte of the connective tissues and blood. Within the monocyte the tubercle bacillus may grow and multiply, while the lymphocyte they found to be intimately connected with limiting the spread of the infected monocytes in the tissues. The predominating reaction within the tissues could be measured in the peripheral blood by the numerical preponderance of either type of cell and might be expressed by the ratio of monocytes to lymphocytes as obtained from a differential smear and total white count.

These observations were soon thereafter confirmed in studies of tuberculous children[2,3] and adults.[4,5,6,7] The results based on supravital and fixed smear determinations demonstrated that in clinical tuberculosis activity was indicated in the peripheral blood by an elevation of the monocyte count. A reversal of the normal ratio of monocytes to lymphocytes indicated extension of the process. When arrest or healing takes place in the tissues the lymphocytes are found to be increased in the circulating blood, the monocytes decreased and a more normal ratio is reëstablished. In the periodic determinations of the leukocytes Medlar[8] stresses the importance of including the polymorphonuclear neutrophil, which he regards as chiefly responsible for tuberculous abscess formation.

In the present study the general leukocytic reaction in various forms of tuberculosis of infancy and childhood was investigated. Attention was directed not alone to the monocyte count and monocyte to lymphocyte ratio, but to changes in the other cell types as well. The supravital technique of Sabin[9] was used throughout to enable examination of the cells in the living state instead of their altered forms after fixation. As shown in a previous study,[10] the percentage of polymorphonuclear neutrophils to lymphocytes is higher with this technique than in the fixed smear. With the supravital method also, cell differentiation is facilitated particularly as it applies to the monocyte and its derivatives, and to the eosinophilic leukocyte.

The monocyte represents the transitional cell of the Ehrlich classification, and includes the large mononuclear cell as well. It is now recognized as a cytologic strain distinct from the polymorphonuclear leukocytes and lymphocytes. In the living preparation after contact with the neutral red dye this cell is found to possess an eccentric nucleus. Near the identation or "hof" of the nucleus are observed fine salmon-tinted bodies arranged usually in a characteristic rosette about an unstained area or centrosphere. Sabin[9] observed that following the ingestion of the tubercle bacillus by the rabbit the monocyte in the circulating blood loses its motility, the number of stainable vacuoles in the cytoplasm is increased and the cell is designated as stimulated or modified. The succeeding

steps in the pathologic transformation of the monocyte are the development of the epithelioid cell and later the Langhans giant cell. The stimulated monocyte and, less frequently, the epithelioid cell were observed in the supravital film in the active cases of this series. In the fixed smear these derivatives of the monocytes cannot be identified.

The present study includes a report of 291 supravital counts on 93 infants and children, 50 of whom served as a normal group. A summary of the results are here presented instead of the analysis of the complete data which will be the subject of a later communication. In general, these studies indicate that an increase in neutrophilic leukocytes and monocytes bears an important relationship to activity and extension of the tuberculous process and that the lymphocyte is associated with resistance.

Normal Group. In analyzing pathologic blood counts the high lymphocytic percentage of normal children must always be considered. Before an increased lymphocytic value in a tuberculous child can be regarded as evidence of healing or resistance, comparison must be made with the blood of a normal child of the same age. Except for the studies of Forkner[11] on newborn infants, the data available for older infants and children with the supravital method are limited. The peripheral blood of 50 normal infants and children was, therefore, examined in 88 determinations on one or more successive days and the average figures were recorded. Each child in this class was negative to 0.2 mg. of tuberculin, and in the group under one year this was carried to 2 mg.

It is observed that the average normal ratio of monocytes to lymphocytes (M/L) increases with age from 0.09 to 1 in infants under one year to 0.25 to 1 in children over the age of four years (Table I, last column). While the control series is small, the averages compare favorably with the estimated normal figures reported by Blackfan and Diamond[3] from fixed and supravital smears.

Acute Tuberculosis. A total of 17 cases comprises this group in all but 3 of which meningitis accompanied miliary tuberculosis. The children varied in age from five months to six years. In this type of tuberculosis the total white count is elevated, especially at the termination. The neutrophilic leukocytes and monocytes are increased while the lymphocytes are decreased. Stimulated monocytes were of frequent occurrence in the blood of the acute cases, but epithelioid cells were observed less often than in the animal experiments. The reason rests, doubtlessly, in the massive doses of organisms experimentally injected into the rabbit as compared with the smaller dosage in human cases. Diagnosis was at times possible from the increased monocytic percentage and the presence of stimulated forms in the peripheral blood previous to the report of other laboratory tests.

TABLE I.—NORMAL FIGURES.

	Age.	Total white count.	Neutrophilic leukocytes.		Eosinophilic leukocytes.		Basophilic leukocytes.		Lymphocytes.		Monocytes.		Monocyte to lymphocyte ratio (M/L).
			Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	
Extremes	2 wks. to 11 mos.	....	....	....	....	....	....	....	....	....	0–10	0–976	0.02–0.24
Average	....	10,175	37.9	3856	3.9	397	0.04	4	53.3	5423	4.9	499	0.09
Extremes	1 to 2 yrs.	....	....	....	....	....	....	....	....	....	6.5–12.0	754–1309	0.12–0.24
Average	....	10,758	34.85	3749	4.63	499	0.17	18	51.12	5499	9.23	993	0.18
Extremes	2 to 3 yrs.	....	....	....	....	....	....	....	....	....	3.5–9.5	404–892	0.09–0.21
Average	....	9,211	45.8	4219	2.82	260	0	0	44.22	4073	7.16	659	0.16
Extremes	3 to 4 yrs.	....	....	....	....	....	....	....	....	....	6.0–9.0	416–885	0.13–0.03
Average	....	9,065	54.17	4913	1.42	128	0	0	37.24	3374	7.17	650	0.19
Extremes	4 to 11 yrs.	....	....	....	....	....	....	....	....	....	6.0–12.0	441–977	0.15–0.37
Average	....	8,167	53.78	4392	5.04	412	0.07	6	32.87	2684	8.24	673	0.25

TABLE II.—DIFFERENTIAL COUNTS IN CASE G. W., ACUTE MILIARY TUBERCULOSIS.

Date.	Remarks.*	Total white count.	Neutrophilic leukocytes.		Eosinophilic leukocytes.		Lymphocytes.		Monocytes.		M/L ratio.
			Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	
12/11	Temperature 104; feedings taken well; child alert	15,340	69.0	10,585	1.0	153	12.0	1841	18.0	2761 (includes 1534 S.M.;† 153 Ep.‡)	1.5
12/13	Temperature 104.4; child still alert	15,200	76.0	11,552	0	0	12.0	1824	12.0	1824 (includes 456 S.M.; 304 Ep.)	1.0
12/15	Temperature 103.2; child drowsy and irrational	21,100	75.0	15,825	0	0	8.0	1688	17.0	3587 (includes 2532 S.M.; 211 Ep.)	2.12
12/16	Drowsy and irrational	22,500	78.0	17,550	0	0	8.0	1800	14.0	3150 (includes 1125 S.M.; 225 Ep.)	1.75

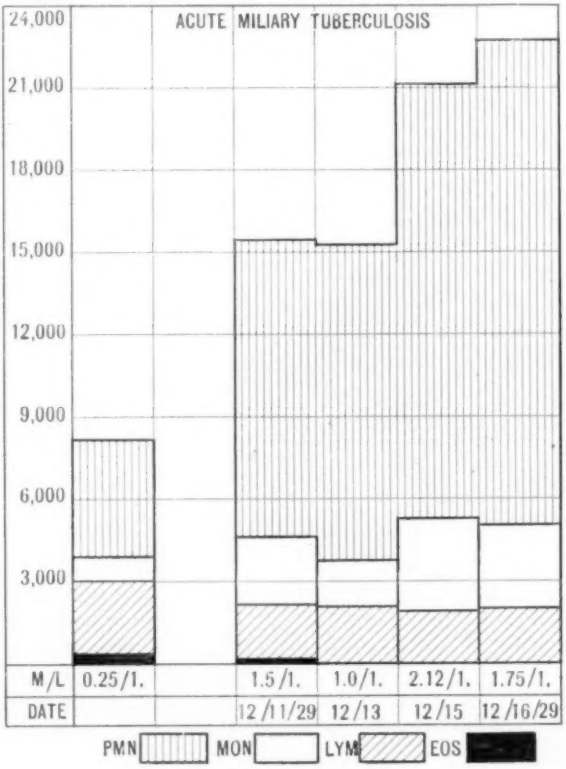
* Died 12/20/29; tuberculin markedly positive 12/4. Roentgen-ray, 12/9, showed generalized miliary tuberculosis. Case uncomplicated by meningitis.

† S.M. = Stimulated monocytes.

‡ Ep. = Epithelioid cells.

The following case illustrates the chief features of this familiar form of tuberculous infection:

Case Report—G. W., a colored female child, aged four years, had been exposed to a tuberculous father. Two months before admission (December 5, 1929) she complained of acute abdominal pain. This symptom in less degree persisted throughout the illness. During this time an evening rise of temperature was noted accompanied by loss of weight, anorexia and loss of energy. In the hospital the child was alert and took her feedings well for the first ten days. Subsequently, she became drowsy, irritable, dyspneic and death occurred fifteen days following admission. Diagnosis: Miliary tuberculosis without meningitis.



Changes in peripheral blood of case G. W., aged four years (see Table II). The first column represents the average normal values for this age group.

Comment. This case portrays the characteristic blood picture of acute miliary tuberculosis. The total white blood count was elevated, the neutrophilic leukocytes and monocytes were increased in both percentages and absolute numbers, the lymphocytes were considerably decreased with a resulting high M/L ratio. Stimu-

‡ Ep. = Epithelioid cells.
† S.M. = Stimulated monocytes.

lated monocytes and epithelioid cells probably active in tissue lesions were present in the circulating blood.

Translated into terms of individual cell function as it applies to tuberculosis, the leukocytosis and increase of polymorphonuclear neutrophiles probably signify a spread of activity as well as a response to the liberation of toxic products, the monocytosis the formation of new tubercles and the fall in lymphocytes, the inability to restrain their multiplication. It is noteworthy that for a time the patient's clinical condition belied the severity of the infection as indicated by the blood smear. This observation is not uncommon, and emphasizes the fact that the blood picture reflects the activity of the tuberculous lesion and neither harmonizes with the clinical appearance of the patient nor with the roentgenographic evidence. It is believed by many observers that with certain restrictions, fluctuations in the blood picture of a tuberculous subject provide a more accurate index of what is taking place in the tissues than can be determined from physical or roentgenologic examinations. An isolated blood count, however, indicates the pathologic state only at the time when the specimen is secured and becomes increasingly valuable by comparison with differential counts taken at other periods.

In this group, the increase in polymorphonuclear neutrophils seemed to occur as a toxic manifestation of the disease. Medlar's view,[8] that this cell responds to abscess formation, may be tenable in the adult form of the disease. It does not apply, however, with equal force to tuberculosis of early life, since abscess formation is rarely present at this age period. The disappearance of the eosinophilic leukocyte occurred almost universally in the fatal cases of this series.

In the acute cases the supravital film frequently gave evidence of pronounced vacuolization and disintegration of the leukocytes with most marked injury to the granulocytes. After an initial phase of increased activity on the part of the polymorphonuclear neutrophil, loss of motility followed and then early disintegration of the cells. The monocytes and lymphocytes were less often affected, whereas the eosinophil shared the fate of the neutrophilic leukocyte. Strands of fibrin became visible and the field seemed to lose its transparency and to take on a ground-glass appearance. This phenomenon was not confined to cases with high fever, but was observed also in cases with a subacute or chronic course in which the temperature was slightly elevated. Vacuolization as well as clumping of the granules in the cytoplasm of the neutrophilic leukocytes have been observed in the fixed smear in infectious diseases and tuberculosis by Mayer.[12] These leukocytic changes may be associated with an immunologic response.[13] The increased fibrin deposit noted in the living preparation may be a counterpart of the increased sedimentation rate observed in tuberculosis[14] for which an increased fibrinogen content of the blood is held accountable.

Subacute and Chronic Tuberculosis. In this group are included 10 cases: 3 of pleurisy, 2 of epituberculous infiltration and 5 extrapulmonary forms, such as erythema nodosum, tuberculous dactylitis, tuberculosis of the spine and ischiorectal abscess with fistula.

The extrapulmonary forms presented in general low or slightly elevated M/L ratios (usually three times as many lymphocytes as monocytes), as well as an absence of stimulated monocytes. In an infant, aged twenty-two months, with erythema nodosum the index was elevated during the period of the eruption and returned rapidly to normal when the skin lesions disappeared.

Tuberculous pleurisy need not necessarily be associated with striking blood changes. In 1 of the cases, however, the period of acute illness was accompanied by an increase of polymorphonuclear neutrophils, a slight decrease of eosinophils and an increased M/L ratio together with stimulated monocytes, constituting the cytologic evidences of activity. With the subsidence of the symptoms and disappearance of the signs, the blood assumed a more normal differential formula.

In 2 cases of epituberculous infiltration periodic blood examinations were often the sole index of changing activity. In 1, a child, aged twenty months, the Roentgen ray picture resembled in many respects that of miliary tuberculosis. The evidence obtained from the examination of the peripheral blood, however, indicated only moderate activity on admission, and the blood count became normal long before the roentgenogram began to clear. In the second case, that of a negro child, aged three years, the pulmonary condition followed closely the description of Eliasberg and Neuland.[15] Death from a probable tuberculoma of the brain ensued six months after the onset of the illness. In the interval the right lung was the seat of massive infiltration, and it was difficult from the Roentgen ray and physical examination to determine the progress of the disease. Blood examination from time to time showed significant deviations from the normal as represented by slight to moderate elevations in the M/L ratio and by an increase in the number of neutrophilic leukocytes. With the advent of the terminal cerebral complication, the monocytes became more numerous, stimulated forms made their appearance, the lymphocytes became fewer, the neutrophilic leukocytes were more prominent and the eosinophils disappeared, the typical picture of marked activity.

Latent Tuberculosis.—In this group have been placed 16 infants and children who reacted positively and usually to intense degree to low dilutions of tuberculin. Many of the children were admitted to the hospital for observation in order to determine the relation of known tuberculous infection to such symptoms as cough, undue fatigue, convulsions and gastrointestinal disorders. A small number were out-patient cases whose only abnormality was the positive tuberculin reaction.

In the ambulatory patient of this group information of practical value may be derived from blood examinations taken at regular intervals. Knowing what the count has been when the child was well, fluctuations in the different cell types during intercurrent illnesses of varying severity, provide a sensitive index of the response to the infection. While an upper respiratory infection in a positive tuberculin reactor may produce slight alterations in the blood picture, it may at times evoke a leukocytic reaction similar to the acute forms of the disease already discussed. These changes, however, do not persist for any length of time, but when present serve as a useful guide in the management of the child's illness. It should be mentioned that the blood of a positive reactor during periods of inactivity may differ in no wise from that of the child who is not sensitive to tuberculin. During the height of a positive tuberculin reaction the peripheral blood usually shows a variable increase in neutrophilic leukocytes and monocytes, a decrease in lymphocytes and a higher M/L ratio.

The pathogenesis of the peculiar changes that take place in the lung adjacent to tracheobronchial nodes infected with tubercle bacilli, so prominent in this group, and which are reflected in the peripheral blood, may be explained in two ways: It may be related to the liberation of a toxin from the tissues injured by the tubercle bacillus or as a result of a chemical constituent of the organism itself. In the chemical analysis of this organism protein and phosphatid fractions have been isolated. Sabin and Doan[16] tested these substances biologically and found that the protein fraction produces a severely toxic state, marked febrile disturbances and an increase in the blood of the neutrophilic leukocytes. The lipoid fraction, on the other hand, was nontoxic and was associated with a rise of monocytes and the development of epithelioid and Langhans giant cells. These cellular responses to the individual chemical fractions of the tubercle bacillus may account in part for different blood pictures that accompany the various clinical forms of tuberculosis.

In one-half of the cases of the latent group the eosinophils ranged from 7 to 14 per cent, values definitely above normal. The agents usually responsible for eosinophilia were eliminated, and the only common factor was sensitiveness to tuberculin. Since the eosinophilic leukocyte is usually linked with allergic states, the quantitative alterations in this type of cell might be considered to vary directly with the degree of allergic hypersensitivity. In the past sensitiveness to tuberculin has been regarded as coëxistent with immunity. In the present series, in states of marked activity particularly in children whose illness was fatal, the fall in the number of eosinophils and often their complete disappearance occurred so frequently, that this change might be regarded as a sign of failing immunity. On the other hand, it cannot be stated from the results here reported that the stage of resistance is invari-

ably accompanied by an eosinophilic increase. The latter observation bears out in part the recent investigations of Rich,[17] who maintains that the terms "allergy" and "resistance" cannot be used interchangeably in tuberculosis.

According to the views of Sabin, the monocytes and their derivatives are the hosts for the tubercle bacillus. A persistently elevated monocyte count may, therefore, be construed as providing a ready vehicle for the dissemination of tuberculosis in the tissues. Experimentally, Doan and Sabin[18] have found that rabbits whose blood had a high preinfection M/L ratio manifested decreased resistance to the injection of bovine tubercle bacilli as contrasted with animals whose ratio was low. A problem worthy of investigation is to determine whether this high initial M/L ratio is present in races or families especially susceptible to tuberculosis. Studies are now in progress which have as their object the correlation of the immunity of the contact child with a negative tuberculin reaction and his blood picture. The results of this study will be included in the elaborated analysis of the cases of the present series which will appear in a later paper.

Discussion. From the data presented in this study, it is apparent that analysis of the complete blood picture serves a useful purpose in determining the status of the pathologic lesion in tuberculosis of infancy and childhood. While it is probably true that in human tuberculosis an increase in monocytes implies dissemination of the tubercle bacillus, it must be emphasized that the blood smear does not make the diagnosis of the disease. Increased monocytes have been found in a variety of nontuberculous conditions, although not at the high levels observed in the acute forms of tuberculosis. Epithelioid cells, more nearly specific for this disease, appear also in Hodgkin's disease.

Cognizance must be taken of the contention of Medlar,[8] that there is no unique leukocytic formula that is pathognomonic of tuberculosis. Every type of cell that responds at some stage to tissue injury by the tubercle bacillus is also called out in other inflammatory processes. When, however, the diagnosis has once been established differential counts taken periodically supply information which derives its value from the evidence now available of the rôle of each of the major white cells in the pathogenesis of the tuberculous lesion.

Confirmatory evidence has been obtained for the principle that regression and progression of the anatomic lesion are reflected in the circulating blood. These phases can be detected in the blood smear by identification of certain qualitative changes in the monocyte together with the individual fluctuations in the percentage and absolute numbers of this cell strain and of the polymorphonuclear neutrophil, eosinophil and lymphocyte. These determinations often afford the sole indication of changes in the course of the

infection and may antedate other diagnostic observations. In general, it may be stated that careful studies of the blood by the newer methods contribute materially in the complete investigation of all patients and are of particular value in studying the progress of the disease in tuberculous patients.

Conclusions. The blood picture of a tuberculous infant or child may be correlated with activity of the pathologic lesion in the tissues and organs.

The complete picture of activity in tuberculosis of infancy and childhood as manifested by the peripheral blood comprises the following: An increased white cell count, an elevation of polymorphonuclear neutrophils and monocytes, a drop in the number of eosinophils and lymphocytes and a rising monocyte to lymphocyte (M/L) ratio. Stimulated monocytes and less often epithelioid cells are usually observed in the supravital film only in the most acute cases. A reversion to a more normal blood picture is found in the stages of resistance and healing.

The trend of the disease may be ascertained from a numerical comparison of the different white cells determined periodically, with emphasis on the monocyte to lymphocyte ratio. Such an examination often furnishes the earliest indication of a change in the status of the disease in the young tuberculous patient.

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THE PERCENTAGE OF EOSINOPHILS IN BLOOD SMEARS FROM INSULIN-TREATED DIABETICS.

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Since its inception in 1922 insulin has been found to give rise to several interesting and more or less important effects apart from its specific action upon carbohydrate metabolism. For instance, Lawrence and Buckley[1] discovered an eosinophilia in 10 out of 20 diabetics who were receiving insulin. Twelve diabetics who were not being so treated, with a single exception, did not show an abnormal number of eosinophils in blood smears. No strictly valid explanation could be offered to account for the occurrence of eosinophilia in the insulin-treated cases. The degree of eosinophilia bore no relation to the amount of insulin which the patients were receiving, although one insulin-resistant case reported by Lawrence,[2] on 200 units of insulin a day, provided the highest figures (12 to 20 per cent of eosinophils). This patient happened to be suffering from slight acne rosacea which, however, was discounted as a cause of the eosinophilia.

Whereas no factor other than the administration of insulin could be found to explain adequately the eosinophilia in the cases mentioned above, the authors have discussed the various possible ways in which this therapeutic agent might be responsible for the phenomenon. The physiologic action of insulin and the possibility of an allergic reaction were dismissed as being very improbable causes. The most likely explanation, according to the investigators, would seem to be irritation of the skin, occasioned by repeated subcutaneous injections of insulin. The eosinophilia found in insulin-treated diabetics would be analogous, therefore, to that frequently encountered in certain skin diseases.

The findings of Lawrence and Buckley suggest an added cause for eosinophilia as well as an interesting by-effect of insulin therapy.

In view of the fact that only a small series of observations were reported by them, and since no further contribution bearing upon the problem has been forthcoming, additional information may be opportune.

Present Investigation. The following study was made for the purpose of corroborating, if possible, the reports of Lawrence and Buckley and also to determine what changes, if any, occurred in the leukocytes in diabetes as disclosed by differential blood counts. Insofar as the eosinophils were concerned, it soon became apparent that eosinophilia was by no means such a commonly occurring incident in patients receiving insulin as the records of Lawrence and Buckley might indicate. Therefore, an answer to the question, "Does eosinophilia occur in insulin-treated diabetics?" was sought.

Seventy differential blood counts were carried out on 43 diabetic patients who were receiving insulin. As a control series, 22 counts were made on 20 diabetics who were not having insulin. The blood smears on which the counts were made were taken at different times of the day and at different seasons of the year. They were stained immediately after being obtained with a good quality Wright's stain. The technique included the use of buffered distilled water in diluting the stain and washing the smears, as suggested by the Feemsters.[3] All counts were made by the same observer. In the great majority of cases 500 white blood cells were counted; several portions of each smear thus were covered.

Results. The generally accepted normal range for eosinophils in blood smears is from 1 to 4 per cent of the leukocytes.[4] Nicholson[5] gives 2 to 5 per cent as representing the normal limits. The eosinophil percentages obtained in the insulin-treated group and in the noninsulin-treated group of patients are shown in Tables 1 and 2 respectively.

Insulin-treated Cases. This group includes patients with diabetes mellitus of various grades of severity who have been taking insulin from 1 to 4 times a day for periods of 1 day to 6 years. Of the 43 cases 9 showed percentages of eosinophils above 4. Of these 8 were above 5 per cent but only 1 above 8 per cent. As can be seen in Table 1, the majority of these cases provided figures which were but slightly above the normal. In only 1 case (No. 31) was frank eosinophilia present. Before starting the use of insulin, this patient showed 1 per cent of eosinophils in blood smears. Four weeks after taking 3 injections of insulin a day an eosinophilia of 12.6 per cent was discovered. One week later the count had gone up to 17.6 per cent, but after another week it had dropped to 10.8 per cent. This patient exhibited no local or general cutaneous reactions and responded well to the treatment. There was no apparent cause for the eosinophilia other than the use of insulin. Case 2 showed during the month of June an eosinophilia of 6.4 per

TABLE 1.—PERCENTAGE OF EOSINOPHILS IN INSULIN-TREATED DIABETICS.

Case No.	Age, yrs.	Sex.	Date.	Eosinophils, per cent.	Duration of insulin treatment.	Number of injections of insulin per day.	Units of insulin per day.
1	32	M	June 18, 1929	2·0	6 yrs.	3	70
			Jan. 8, 1930	1·6	6½ yrs.	3	55
2	18	F	June 19, 1929	6·4	2 yrs.	2	32
			Dec. 11, 1929	1·2	2½ yrs.	2	42
3	13	F	June 20, 1929	1·8	3 yrs.	3	48
			Dec. 27, 1929	1·8	3½ yrs.	3	45
4	16	F	June 22, 1929	3·4	2½ yrs.	2	45
			Jan. 10, 1930	2·4	3 yrs.	3	55
			Jan. 9, 1931	1·4	4 yrs.	3	46
5	60	F	June 25, 1929	1·0	3½ yrs.	2	15
			Jan. 4, 1930	1·8	4 yrs.	2	15
6	54	F	June 28, 1929	2·8	1 yr.	1	10
			Dec. 29, 1930	5·2	2½ yrs.	3	38
			Jan. 9, 1931	2·6	3½ yrs.	0	0
7	12	F	June 26, 1929	1·6	2 mos.	3	35
			Dec. 13, 1929	3·8	8 mos.	3	50
8	48	M	June 29, 1929	1·2	4 yrs.	2	15
9	24	F	Dec. 8, 1929	0·4	6 mos.	2	25
10	25	M	Dec. 10, 1929	...	3 yrs.	3	70
			(10.30 A.M.)	1·4			
			(4.00 P.M.)	3·2			
			Dec. 24, 1929	...	3 yrs.	3	80
			(10.00 A.M.)	4·0			
			(11.30 A.M.)	2·0			
			(2.15 P.M.)	2·0			
			(5.00 A.M.)	1·0			
11	5	F	Dec. 10, 1929	3·0	3 wks.	3	28
			Jan. 14, 1931	1·0	1 yr.	2	16
12	14	M	Dec. 11, 1929	2·8	3 yrs.	3	80
13	52	M	Dec. 12, 1929	5·6	6 mos.	3	35
			Jan. 15, 1931	4·4	1½ yrs.	3	60
14	40	F	Dec. 13, 1929	3·4	5½ yrs.	3	40
			Jan. 10, 1930	2·2	5½ yrs.	3	55
			Jan. 2, 1931	0·2	6½ yrs.	3	74
15	67	F	Dec. 13, 1929	2·2	1 yr.	2	45
			Jan. 6, 1931	1·6	2 yrs.	2	50
16	70	M	Dec. 17, 1929	1·0	5 yrs.	2	20
			Jan. 15, 1930	4·6	5 yrs.	2	20
17	60	F	Dec. 17, 1929	3·2	2 yrs.	3	45
			Dec. 26, 1929	...	2 yrs.	3	45
			(10.15 A.M.)	2·0			
			(4.00 P.M.)	4·0			
18	50	M	Dec. 26, 1929	2·8	6 yrs.	2	35
19	49	M	Dec. 26, 1929	2·0	2½ yrs.	2	45
20	4	M	Dec. 27, 1929	1·4	1 yr.	2	8
21	50	F	June 21, 1929	6·8	0	0	0
			Dec. 30, 1929	8·0	6 mos.	2	8
			Jan. 25, 1931	5·0	1½ yrs.	2	18
22	50	F	Jan. 8, 1930	1·8	6 mos.	1	5
23	55	M	Jan. 9, 1930	1·4	3½ yrs.	2	22
24	14	F	Jan. 17, 1930	3·0	6 mos.	3	35
			Jan. 9, 1931	5·8	1½ yrs.	3	60
25	60	F	Dec. 16, 1930	0·8	2½ yrs.	3	40
26	22	M	Dec. 16, 1930	0	2 mos.	2	18
27	49	M	Dec. 16, 1930	0·4	0	0	0

TABLE 1.—PERCENTAGE OF EOSINOPHILS IN INSULIN-TREATED DIABETICS. (*Continued.*)

Case No.	Age, yrs.	Sex.	Date.	Eosinophils, per cent.	Duration of insulin treatment.	Number of injections of insulin per day.	Units of insulin per day.
			Feb. 6, 1931	2 4	3 wks.	3	52
28	68	F	Dec. 19, 1930	2 4	1 mo.	2	22
29	30	F	Dec. 19, 1930	2 0	6 mos.	4	84
30	62	F	Dec. 21, 1930	1 0	5 days	2	18
31	50	F	Dec. 29, 1930	1 0	0	0	0
			Jan. 30, 1931	12 6	4 wks.	3	38
			Feb. 6, 1931	17 6	5 wks.	3	38
			Feb. 13, 1931	10 8	6 wks.	3	42
32	52	M	Dec. 30, 1930	0 2	0	0	0
			Jan. 3, 1931	6 4	4 days	2	36
33	69	F	Jan. 6, 1931	3 8	1 day	2	20
			Jan. 30, 1931	4 2	3 wks.	2	36
34	17	M	Jan. 9, 1931	2 0	6 yrs.	3	64
35	42	F	Jan. 9, 1931	0 6	4 yrs.	3	30
36	65	F	Jan. 10, 1931	6 0	3 mos.	1	10
37	65	F	Jan. 10, 1931	1 4	3 wks.	1	15
38	65	F	Jan. 17, 1931	2 4	1 yr.	2	16
39	62	F	Jan. 20, 1931	0 8	6 wks.	3	42
40	12	M	Feb. 6, 1931	1 8	3 yrs.	3	58
41	13	M	June 21, 1929	5 4	0	0	0
			Dec. 28, 1929	1 8	0	0	0
			Jan. 31, 1931	3 2	1 yr.	2	46
42	60	F	Feb. 9, 1931	3 0	3 wks.	3	64
43	13	F	Feb. 18, 1931	3 6	1 mo.	2	24
Av.	..	..	....	3 0		(70 counts	

TABLE 2.—PERCENTAGE OF EOSINOPHILS IN NONINSULIN-TREATED DIABETICS.

Case No.	Age, yrs.	Sex.	Date.	Eosinophils, per cent.
1	50	F	June 17, 1929	1 6
2	68	F	June 24, 1929	1 8
3	47	M	Dec. 13, 1929	2 0
4	79	M	Dec. 13, 1929	3 4
			Jan. 3, 1931	3 8
5	60	M	Dec. 17, 1929	6 4
6	55	F	Dec. 19, 1929	1 4
7	43	F	Dec. 21, 1929	0 8
8	30	M	Dec. 21, 1929	3 4
9	50	F	Jan. 1, 1930	10 6
10	37	F	Jan. 10, 1930	3 1
11	50	F	Jan. 10, 1930	3 6
12	70	F	Dec. 16, 1930	2 8
13	57	F	Dec. 19, 1930	4 4
14	75	M	Dec. 24, 1930	2 6
15	65	M	Oct. 1, 1930	1 0
			Jan. 5, 1931	2 0
16	68	M	Jan. 10, 1931	1 2
17	34	M	Jan. 29, 1931	0 2
18	65	F	Jan. 29, 1931	1 2
19	60	M	Feb. 5, 1931	3 0
20	51	F	Feb. 5, 1931	4 6
Average (22 counts)				2 9

cent. At that time the patient was in the midst of one of her annual "hayfever" attacks. Six months later, when no "hayfever" symptoms existed, there was 1.2 per cent of eosinophils. Case 21 showed an eosinophilia of 8 per cent 6 months after taking 2 injections of insulin per day and 5 per cent after another year of similar treatment. But this patient had 6.8 per cent of eosinophils in her blood while under treatment by diet alone before commencing the use of insulin. Cases 17 and 33 had marked skin reactions, due to the insulin injections, yet no eosinophilia was observed. Comparison of the eosinophil percentages before with those obtained after the commencement of the use of insulin in Cases 27, 32 and 33 shows that a slight increase did occur. However, in none of these was the increment great enough to place them within the scope of definite eosinophilia. The fact that fluctuations in the eosinophil percentages occur from time to time during the day, as exemplified in Case 10, must be taken into account when interpreting the significance of these slight increases. The average for the whole group was 3 per cent of eosinophils. Apart from the one high case, the range was from 0 to 8 per cent.

Noninsulin-treated Cases. Twenty-two differential blood counts on 22 diabetics who were being treated by diet alone without insulin, disclosed results (Table 2) which did not differ appreciably from those obtained in the insulin-treated group. Two cases showed eosinophil percentages of 6.4 and 10.6, for which no explanation was discovered. The remaining 18 cases gave figures between 0.2 and 4.4 per cent. The average for the group was 2.9 per cent.

Discussion. While eosinophilia may result from repeated injections of insulin, it is by no means a commonly occurring incident, at least under the conditions of the present investigation. Only one patient was followed with any degree of regularity following the commencement of insulin therapy. It is possible that eosinophilia may have been temporarily present in others of this series but not discovered by a single blood examination or by counts made at long intervals after beginning the use of insulin. The investigation is being continued, however, with these points in mind. No attempt is made to explain the discrepancy in the results obtained by Lawrence and Buckley and those recorded here. To ascribe the lack of agreement to any such factors as differences in insulin dosages, brand of insulin, locality or climatic conditions would be mere speculation. It is of interest to note, in this regard, that Lawrence and Buckley observed an increase in the eosinophilia in several cases during the very hot weather of the summer months, the counts being lower before and after that time.

Reference to eosinophilia ordinarily recalls the association of this phenomenon with allergic and anaphylactic states, certain skin lesions and protozoal infestations. The medical literature of the

past several years supplies instances of reactions to insulin which are unrelated to changes in the blood-sugar concentration and apparently independent of any hormone activity. Such reactions may be local or general in character. They may be limited to the region surrounding the site of injection, and consist of erythema with varying degrees of localized induration and swelling. More serious types of reaction may occur, manifesting themselves by generalized urticaria and edema or by gastrointestinal symptoms, as in a case reported recently by Williams.[6] Reactions such as those referred to above were not infrequent apparently during the early days of insulin usage. They could be attributed in all probability to protein contained in the original insulin preparations. Improved methods of purification and concentration soon obviated these untoward effects to a large extent.

That a specific hypersensitiveness to insulin *per se* may exist is suggested by the immunologic studies of Tuft.[7] This particular type of hypersensitiveness is probably analogous to the so-called drug idiosyncrasies. Another variety of hypersensitiveness also can occur in spite of adequate purification and concentration of insulin and is evidently dependent upon some factor contributed by the source of supply of the product. For example, a patient may be intolerant to insulin derived from the pancreas of the pig, yet experience no ill effects from insulin prepared from beef pancreas, as in the case described by Williams.[6] No eosinophilia was noted in this case, however. A similar example of insulin intolerance is mentioned by Tuft.[7] The case of a patient who exhibited local reactions to insulin at the commencement of treatment, with the subsequent disappearance of the reactions, is reported by Lasersohn.[8] No mention is made regarding the blood counts by the two latter observers.

In view of these data alone, the occurrence of eosinophilia during insulin therapy is by no means an improbability. If it does occur, its cause will possibly be found in some more subtle influence than mere repeated punctures of the skin by the hypodermic needle. In the meantime the question, "Does eosinophilia occur in insulin-treated diabetics, and if so, why?" is wanting an answer.

Summary. Eosinophilia is not a generally occurring incident in diabetics receiving insulin treatment. Its presence in some cases must be admitted. Seventy differential blood counts from 43 diabetics receiving insulin revealed a definite eosinophilia in only 1 case. This low incidence of eosinophilia under such conditions is not in accord with the findings of previous investigators. No explanation is offered for the discrepancy in the results. The average percentage of eosinophils in 43 diabetics receiving insulin was not appreciably different from the average percentage of eosinophils in 20 diabetics who were treated by diet alone without insulin.

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FURTHER STUDIES IN A CASE OF CALCIFICATION OF SUBCUTANEOUS TISSUE ("CALCINOSIS UNIVERSALIS") IN A CHILD.*

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In 1926 Wilens and Derby[1] reported a case of "calcinosis universalis" seen at the Children's Hospital, Boston. Recently we have had the opportunity of observing this same patient for a prolonged period in the research ward of the Massachusetts General Hospital. It was hoped that a more detailed study of this patient might throw further light on the underlying cause of this obscure condition. Accordingly, we undertook a study of the calcium, phosphorus and nitrogen metabolism in conjunction with chemical and histologic examinations of biopsied material.

Case Report. B. R. C., M. G. H. No. 300059, a white American schoolboy, aged 10.5 years, was admitted to the metabolism ward of the Massachusetts General Hospital on April 2, 1930.

A study of the *family history* revealed no known tendency to chronic disease. No relatives had been known to have a condition similar to that of the patient.

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The *past history* showed that the child's birth (on November 27, 1919) had been normal, that he was breast fed for 2 months and then was given Mellin's food. He gained normally. His first tooth was acquired when 9 months of age, and he walked at about 18 months. At the age of 2 years he had pertussis and four convulsions of unknown etiology; at 3 years he had bronchopneumonia; at 4 years, lobar pneumonia; at 5 years, measles and scarlet fever; at 7 years, mumps; at 9 years, septic sore throat.

The *present illness* began about 8 years ago, when the patient was between 2 and 3 years of age. At this time his mother noticed that his legs appeared weak and that he dropped to his knees when attempting to walk. About 7.5 years ago several small painless swellings appeared on the crest of both tibæ. Later similar hard swellings appeared under the skin in various places over the body. Six years ago, apparently for the first time, it was noticed that calcareous material was extruded from the swellings over the left tibia. About 4 months after this occurrence one of the swollen areas began to discharge puriform liquid along with chalky material.

Five and a half years ago he was admitted to the Children's Hospital because of acute swelling and tenderness in the region of the left knee. At that time the serum calcium and phosphorus were found to be normal. The subcutaneous nodules were examined histologically. Chemical analysis revealed the presence of calcium salts. These findings have been reported.[1]

One and a half years ago he was again admitted to the Children's Hospital because of acute pain and swelling in the region of the right elbow. A note made at that time stated that since his first admission there had been no important change in his condition.

Nine months ago (July 7, 1929) he was admitted to the Massachusetts General Hospital on the surgical service. At that time the abscesses in the skin and subcutaneous tissue over the left elbow were incised and drained. Three months later he was again admitted to the surgical service of the Massachusetts General Hospital because of abscesses about calcareous nodules over the left elbow and both knees.

In the weeks just preceding the hospital admission with which this present paper is concerned the patient had continued about as before. New calcareous nodules had formed in various places over the body, older ones had been extruded through the skin from time to time. On several occasions particularly abundant accumulations of the chalky material in the tense soft tissue covering joints had given rise to acute pain and swelling. Where partly extruded nodules had become secondarily infected superficial abscesses had formed and pus had been discharged along with the calcareous material.

Physical examination in the ward showed a poorly developed and poorly nourished boy. He looked chronically ill. His facial expression and speech were those of an older individual. His teeth were poor; those in front, particularly above, showed notched margins and serrations across them about midway from gum to free border. The tonsils were moderately enlarged and scarred. No glands were felt except for several swollen, discrete, nontender nodes along the anterior border of the sternocleidomastoid muscle on each side. Many hard subcutaneous nodules were present in various places. These nodules were composed of white or yellowish-white chalky material. Their size varied from the smallest possible up to 1 cm. or more in diameter. In several areas two or more fairly large nodules had coalesced to form a much larger accumulation of calcareous material. The nodules were most numerous on the extremities, particularly about the knees, elbows and anterior aspect of the legs. It is worthy of note that these lesions were entirely absent over the scalp, thorax and abdomen. There were lesions in all stages of development from nodules completely covered by intact skin to those just breaking through

and extruding the chalky material (with open, shallow ulcerations in some places) to the final scars. Small superficial ulcers in various stages of breaking down and healing were present over both knees, the left foot, the buttocks and both elbows. None of the joints were swollen, red, hot or tender. Some were partly ankylosed because of the extensive accumulation of calcareous material about them. The right thigh could be flexed only to make an angle of about 90 degrees with the trunk. Motion at the right knee was limited. The lower leg could be flexed to make a 90-degree angle with the thigh and could be extended to within 35 degrees of full extension. Because of this partial ankylosis of the right knee joint, the boy walked with a limp. The right arm could be abducted about 45 degrees. Motion was limited at both elbows. Complete extension of the right arm was lacking by 15 degrees; flexion was but slightly limited. Extension of the left arm was normal, but flexion was limited about 30 degrees.

Laboratory Data. The urine was normal except for the presence of a slight trace of albumin. On admission his erythrocyte count was 4,500,000; leukocyte count, 8250 and hemoglobin (Tallquist) 65 per cent. The blood smear was normal, except for a 7 per cent eosinophilia. Two months later the erythrocyte count was 5,000,000; leukocyte count, 10,100; hemoglobin (Tallqvist), 80 per cent, and the blood smear was normal. A blood Hinton test was negative. The blood sugar was 105 mg. (fasting); nonprotein, nitrogen 30 mg., and uric acid, 1.2 mg. per 100 cc. The blood cholesterol was 120 mg. per 100 cc. The carbon dioxid combining power of the blood was normal (57.1 vols. per cent). The blood serum calcium and phosphorus were always found to be normal. The basal metabolic rate was on one occasion +16 as predicted on height and +34 as predicted on weight (Talbot special standard).

Roentgen Ray Report. The following interpretation of the roentgenograms was submitted by Dr. A. O. Hampton: "Examination included anteroposterior and lateral views of the entire skeleton. An effort was made to show both the soft tissues and the bone structure. Calcium deposits were diffusely scattered in the subcutaneous tissues of the arms, legs, buttocks and axillæ. The scalp, neck and chest were essentially normal. The calcium deposits were most pronounced in the right arm and right thigh. Of the joints, the tissues of the knees and elbows showed the greatest deposits of calcium. The shape and size of the calcium deposits varied from 1 mm. to 3 cm. in diameter, except in the region of the right sartorius muscle, the right hamstring muscles and the extensors of the left wrist. In these regions deposits extended nearly the whole length of the muscles and produced a calcium cast of the muscles mentioned. The calcium deposits showed no bone structure, being composed of multiple small irregular granules grouped rather compactly in the larger deposits and appearing fairly discrete in the smaller areas. The joint spaces were preserved and the joint outlines appeared smooth. There was no definite evidence of calcium deposits within any of the joint cavities. The knees showed an unusually dense accumulation of calcium very near or partially surrounding the joint capsule. All of the bones were rather small, thin and the bone trabeculæ were coarse and slightly separated. The cortex of the bones was unusually thin and the medullary canals were preserved. The epiphyses showed no abnormality in time of fusion. The epiphyseal lines were smooth and not so dense as usual. There were no fractures or deformities of any of the bones."

Course in the Hospital. During his stay of 3 months in the ward no essential change was noted in his condition. He was up and about practically all the time except for a day or two following the biopsies. Three times during the 3 months his temperature rose to 100° or above; there were also a few other transient temperature rises to less than 100°. These

periods of fever were associated with acute swelling and tenderness about one or more of the nodules. The biopsy wounds healed promptly. Orthopedic consultants thought that operative interference with his ankylosed joints was inadvisable. He was discharged unrelieved on July 3, 1930.

I. **Studies of Biopsy Material.** On April 28, under local anesthesia, a subcutaneous nodule was removed from each thigh by Dr. V. P. Williams. A portion of this material was preserved for histologic study and the rest used for chemical analysis.

Chemical Studies. *Methods Used.* 1. Uric Acid.[2] 180 mg. of the wet samples were transferred to a 25-cc. volumetric flask. To this were added 5 cc. of 10 per cent sodium tungstate and 5 cc. of two-thirds normal sulphuric acid. The total volume was then made up to 25 cc., the flask shaken and the contents poured on to a filter. Uric acid was determined on the filtrate according to the method of Benedict.[3]

2. Cholesterol and Fatty Acids.* 3.0623 gm. of wet sample were extracted continuously for 36 hours in a Soxhlet apparatus (with alcohol for 24 hours and with ether for 12 hours). After extraction the dried residue was found to weigh 1.5373 gm. Cholesterol and fatty acid were determined on the combined alcohol and ether extracts according to the method of Bloor.[4]

3. Calcium and Phosphorus. One-tenth gm. of the above dried material was weighed into an evaporating dish. This was ashed over a free flame and finally in an electric muffle furnace. The ash was dissolved in a few cubic centimeters of 50 per cent hydrochloric acid and the volume was made up to 100 cc. In this solution calcium was determined by the method of Fiske[5] and the phosphorus by that of Fiske and Subbarow.[6]

4. Carbon Dioxid.† This was determined on the dried material by the method outlined by Shear and Kramer.[7]

The following values were obtained:

	Wet material, gm. per 100 gm.	Dry material, gm. per 100 gm.
Water	49.80	
Uric acid	.00417	
Cholesterol	.415	
Fatty acid	1.061	
Calcium	..	27.60
Phosphorus	..	12.75
Carbon dioxid	..	4.09

The above figures show a low uric acid content. The value is higher than that obtained by Folin, *et al.*,[2] for the muscle of normal dogs (1.2 to 2.5 mg. per 100 gm.) and normal rabbits (1.2 to 1.4 mg. per 100 gm.), but it is certainly low enough to preclude any possibility that the concretions were composed of urates.

Because of the lack of comparable data in the literature, we are unable to properly interpret the values obtained for cholesterol and fatty acids. However, they are no greater than one might expect with the amount of normal tissue breakdown involved in pathologic calcification.

The values obtained for calcium and phosphorus are quite in accord with those reported for pathologic calcification by previous

* We are greatly indebted to Dr. E. R. Lenherr, of the New England Deaconess Hospital Laboratory, for the cholesterol and fatty acid determinations.

† We wish to thank Dr. L. T. Fairhall for the determination of carbon dioxid.

workers. Gascard,[8] in 1900, in a brief note gave the results of an analysis of hard subcutaneous tumors removed at autopsy from the inner side of the thigh of a young man. Harlay,[9] in 1903, analyzed a portion of a subcutaneous calcareous mass removed from the outer aspect of the right knee of a woman, aged 60 years, with arthritis. After recalculation to provide uniformity these results may be compared with our own as follows:

	Gascard. Per cent.	Harlay. Per cent.	Authors'. Per cent.
Calcium	30.00	31.82	27.60
Phosphorus	13.50	13.04	12.75

In our case if one subtracts the calcium in the form of calcium carbonate from the total calcium content one obtains a calcium to phosphorus ratio quite similar to that found in normal bone. The residual calcium to phosphorus ratio can be calculated according to the formula used by Shear and Kramer.[7] This formula is as follows:

$$\frac{\text{Residual Ca}}{\text{Residual P}} = \frac{\text{Total Ca} - \text{Ca carbonate}}{\text{Total inorganic P}}$$

$$4.09 \times 0.91 = 3.70 \text{ gm. calcium present as } CaCO_3$$

$$\frac{\text{Residual Ca}}{\text{P}} = \frac{27.6 - 3.72}{12.75} = 1.87$$

This value (1.87) compares favorably with the theoretical calcium to phosphorus value of 1.94 for $Ca_3(PO_4)_2$ of normal bone and with the values (1.88 to 2.01) obtained by Kramer and Shear[10] for pathologic calcifications in man.

Histologic Study. The specimen consisted of a number of irregular pieces of skin and subcutaneous tissue. The subcutaneous tissue contained a number of relatively large irregular deposits of an amorphous, white chalk-like material. This material was solid in certain areas, in others it had the consistency of a thick paste.

Microscopic Examination. Paraffin and frozen sections, formaldehyd and Zenker's fixation stains: Hematoxylin and eosin, eosin methylene blue, Klotz' and von Kossa's silver nitrate methods of staining calcium.

Most of the epidermis was thrown into irregular folds. The papillary layer of the epithelium was very irregular, and superficial desquamation of the horny layer was more prominent than normal. In some areas the corium was very dense in structure, although the coil glands and hair follicles distributed throughout this layer appeared normal. In most fields the corium was free of calcareous deposits, although in a few the deposition of calcium had encroached upon the basal layer of the corium. In such fields the fibrous tissue surrounding the calcified masses was intimately fused with the corium.

Several microscopic sections included cross sections of entire calcified subcutaneous nodules. These areas were usually found beneath the corium in the subcutaneous fat. They were filled with irregular masses of varying sizes which stained intensely basic. This material was seen as small, finely divided particles, having a granular appearance, or as larger particles

which were globular or angular shaped. In the preparations stained by the methods of von Kossa and Klotz for the identification of calcium these granular, globular and crystalline masses were stained black. Preparations stained by the method of Klotz for demonstrating calcium in the form of of both phosphate and carbonate showed a positive reaction in a greater part of the deposit than did von Kossa's method of staining calcium phosphate.

In the preparations stained with hematoxylin and eosin and the eosin methylene blue each area of calcification was surrounded by areas of fibrosis. Depending apparently on the age of the calcium deposit, this layer of fibrosis varied from one of dense cellular collagen to one of fibroblastic proliferation and bloodvessel ingrowth. In almost all portions of the sections numerous, irregular giant cells of the foreign-body type could be found about the margins of the calcified masses. No cholesterol crystal clefts were found in any of the calcified areas or within any of the giant cells. Many of the foreign-body giant cells had formed about calcareous particles. Occasional vacuolated endothelial leukocytes (foam cells) were present about the margins of the calcified areas. No bone formation was seen.

The sequence of the pathologic changes leading to the large areas of calcification remained obscure after histologic study. The impression was gained, however, that the initial lesions were represented by those areas in which whole or partial fat lobules were altered by deep basic staining granules. In the least involved areas these granules were seen only around the periphery and in between intact fat cells. (Fig. 9.) Where a more pronounced calcareous deposition had occurred the entire fat cells were granular and stained by basic dye. Other fat cells were entirely obscured by the dense lime deposit. The absence of any evidence of antecedent fat necrosis was a noteworthy feature. A few fields showed a scattering of lymphocytes and polymorphonuclear leukocytes. In areas where the altered fat cells were still recognizable, surrounding fibroblastic proliferation was scant in amount and little collagen had been laid down.

Occasional bloodvessels near the calcified areas showed thickened walls in which hyalinization of the medial coat had occurred. Perivascular infiltration with lymphocytes was noted about a few of the bloodvessels. (Fig. 10.)

Except for the findings of more numerous peripheral giant cells and more complete encapsulation with fibrous tissue, these calcareous lesions showed no important differences from those seen in the sections made in 1926, which we have had the opportunity of studying.

TABLE 1.—DIET AND THERAPY USED DURING METABOLIC STUDIES.

Three-day period.	Type of diet.		Therapy.	
	Calcium.	Phosphorus.	Ammonium chlorid, gm. per day.	Irradiated ergosterol,‡ mg. per day.
1 to 7	Very low	Mod. low*	None	None.
8 to 13	Very low	Mod. low	4†	None.
14 to 16	Very low	Mod. low	6	15
17 to 18	Very low	Mod. low	6	None.
19 to 20	Very low	Mod. low	None	None.
21 to 23	Mod. low*	Very low	None	None.
24 to 26	Mod. low	Very low	6	None.
27 to 28	Mod. low	Very low	None	None.

* Inadequate for a normal child of the patient's age. For actual figures see Table 2.

† For 2 days of Period 12 and during Period 13, 6 gm. a day were given.

‡ Kindly supplied by the Winthrop Chemical Company of New York City.

TABLE 2.—MASTER B. R. C. (AGED 10 YEARS).
(All values are expressed as Average Figures per Three-day Period.)

Periods.	Dates, 1930.	Average weight, kg.	Phosphorus.					Calcium.					Nitrogen.					Diet.					Blood serum.				
			Output.			Intake.	Balance.	Output.			Intake.	Balance.	Output.			Intake.	Balance.	CHO.	Protein.	Fat.	Calories.	Fluid.	Date.	CO_2.	Ca.	P.	Therapy, NH_4Cl, gm. per day.
			Urine.	Feces.	Total.			Urine.	Feces.	Total.			Urine.	Feces.	Total.													
1–7	4/3–4/24	24.2	1.054	.346	1.400	1.826	+.427	.050	.046	.096	.266	+.170	19.2	2.3	21.5	26.2	+4.7	608.1	163.5	156.4	4786	3600	4/24	57.1	10.2	5.8	
8–13	4/24–5/12	24.3	1.465	.321	1.786	1.813	+.027	.429	.047	.476	.264	−.212	25.9	2.2	28.1	26.1	−2.0	598.9	162.7	158.9	4799	3783	5/2 5/9	51.8 51.2	9.9 10.3	5.7 6.2	4*
14–16	5/12–5/21	24.0	1.090	.309	1.399	1.827	+.428	.403	.034	.437	.267	−.170	20.3	2.4	22.7	26.2	+3.5	711.6	163.5	159.0	4932	3900	5/13 5/17	48.8 53.9	10.0 9.5	5.1 5.4	6†
17–18	5/21–5/27	23.8	1.876	.262	2.138	1.827	−.311	.963	.027	.990	.267	−.773	31.0	2.6	33.6	26.2	−7.4	691.6	163.5	159.0	4738	3900	5/22	49.0	9.8	5.6	6
19–20	5/27–6/2	24.1	1.377	.287	1.664	1.827	+.163	.237	.038	.275	.267	−.008	21.3	2.6	23.9	26.2	+2.3	651.6	163.5	159.0	4626	3900	5/27	52.4	8.8	5.3	
21–23	6/2–6/11	24.1	1.466	.200	1.666	1.110	−.556	.186	.043	.229	.666	+.437	20.9	2.5	23.4	24.9	+1.5	711.6	155.7	110.4	4902	3900	6/4	53.4	9.8	6.1	
24–26	6/11–6/20	24.3	1.423	.191	1.614	1.067	−.547	.695	.045	.740	.645	−.095	21.1	2.4	23.5	24.3	+0.8	713.6	151.6	116.4	4754	3900	6/19	46.3	. . .	. . .	6
27–28	6/20–6/26	23.9	0.957	.220	1.177	0.961	−.216	.228	.031	.259	.599	+.340	14.1	2.2	16.3	21.7	+5.4	707.2	135.6	102.0	4289	3750	6/23 6/24	48.4 . . .	9.9	5.6	

* For two days of Period 12, and during Period 13, 6 gm. a day were given.

† Also 15 mg. ergosterol per day.

II. **Studies of Calcium, Phosphorus and Nitrogen Metabolism.** *Methods.* The methods used in the metabolism ward have been outlined in a previous paper.[11] All diets were carefully calculated and weighed, fluids carefully measured and excreta saved in 3-day periods. Determinations of calcium were done according to the method of Fiske;[5] phosphorus, that of Fiske and Subbarow;[6] carbon dioxid combining power, that of Van Slyke;[12] total nitrogen, the Kjeldahl method.[13] These studies were carried out for 12 weeks. This enabled us to detect whether or not there was any gross deviation from the values obtained in a study of normal individuals under similar conditions.[14] It also allowed us to note the effect of dietary changes and various forms of therapy. The table below briefly outlines the various conditions under which the patient was studied. One should note the divisions of this study and the number of periods included in each division.

In Table 2 the metabolism data are presented. It will be observed that the values are expressed as the average of all the periods that comprise that particular division of the study. It will be seen that during the control periods, 1 to 7 (21 days), on an inadequate calcium intake (0.266 gm. per 3-day period), the urinary calcium was 0.050 gm. and the fecal calcium was 0.046 gm., making a total output of 0.096 gm. with a resulting *positive* calcium balance of +0.170 gm. per 3-day period. These values are definitely abnormal as compared with those obtained from normal adult individuals studied on a similar diet. In their series of 13 normal adult subjects Bauer, Albright and Aub[14] found the average calcium excretion on the same low calcium diet to be 0.79 gm. (urinary 0.6 gm. plus fecal 0.19 gm. per 3-day period), resulting in a *negative* calcium balance of 0.46 gm. These figures were obtained on adults, to be sure, but in 2 essentially normal boys, aged 9 and 14 years, we obtained the following results while using this same low calcium diet:

TABLE 3. — AVERAGE VALUES PER 3-DAY PERIOD ON TWO APPARENTLY NORMAL BOYS.

	Case 1.	Case 2.
Age, yrs.	14	9
Calcium:		
Urine	0.181	0.176
Stool	0.290	0.225
Total output	0.471	0.401
Intake	0.240	0.280
Balance	−0.231	−0.121
Phosphorus:		
Urine	2.175	1.100
Stool	0.434	0.460
Total output	2.609	1.560
Intake	2.667	1.910
Balance	+0.058	+0.350
Number of 3-day periods averaged	3	6

Thus one notes that in the case under discussion both the urinary and fecal calcium excretions were definitely lower than in either of the two apparently normal boys studied. These excretions were sufficiently low to enable the patient to maintain a *positive calcium balance* in spite of the *extremely low-calcium intake.* He excreted approximately 0.4 gm. less calcium per 3-day period than did Case 1 and approximately 0.3 gm. less than Case 2. The low fecal and urinary calcium excretions indicate that there may have been increased absorption and that there was increased retention. If the calcium absorbed had not been retained the urinary calcium value would have exceeded the value observed in normal individuals. Actually, there occurred an accompanying decrease in the urinary

calcium excretion. This finding further emphasizes the ability of the tissues of this patient's body to retain calcium.

This same bodily retention is evident in the case of phosphorus. The 3-day intake was only 1.826 gm., the urinary excretion was 1.054 gm., the fecal excretion, 0.346 gm., and the resulting balance, a positive one to the extent of 0.427 gm. per 3-day period. The phosphorus balances for Cases 1 and 2 were +0.058 gm. and +0.350 gm. respectively. (Table 3.)

The average values for Periods 8 to 13 (18 days), during which ammonium chlorid was given, show that the urinary calcium was increased more than eight times that obtained in the control periods, so that the final calcium balance was −0.212 gm. per 3-day period. Phosphorus shared in this increased excretion with the production of a final balance of +0.027 gm. per 3-day period as contrasted with the control value of +0.427. In the case of both calcium and phosphorus this larger output was entirely urinary. The fecal calcium was essentially the same during the medication periods as in the control periods. The fecal phosphorus was slightly less during the medication period. Thus the administration of ammonium chlorid resulted in the mobilization of calcium and phosphorus in a manner similar to that seen in other individuals.[15]

During Periods 14 to 16 (9 days) the low calcium diet and ammonium chlorid were continued, but in addition 15 mg. of irradiated ergosterol were administered daily by mouth. During the administration of irradiated ergosterol the fecal calcium fell from 0.047 to 0.034 gm. The urinary calcium was reduced from 0.429 to 0.403 gm. These changes resulted in a reduction of the negative calcium balance from −0.212 to −0.170 gm. The fecal and urinary phosphorus were likewise diminished. The former decreased from 0.321 to 0.309 gm., the latter from 1.465 to 1.090 gm. The positive phosphorus balance increased from +0.027 to +0.428 gm. We have observed[16] a similar decrease in the fecal calcium and phosphorus accompanied by a diminution of the urinary calcium and phosphorus when irradiated ergosterol was administered to individuals with calcium deficiency diseases. In the present case the fecal excretions of calcium and phosphorus were only slightly influenced. The effect on the urinary excretions was more pronounced in the case of the phosphorus. Failure to obtain a greater decrease in the fecal excretions may have been due to the fact that the fecal values were abnormally low before irradiated ergosterol therapy was instituted. This unusual finding is seemingly a manifestation of the disease under discussion. The irradiated ergosterol effect is best interpreted as an increased retention of both elements. Therefore, irradiated ergosterol administration in this instance accentuated the already existing abnormality of calcium metabolism, namely, increased absorption from the intestinal tract and increased retention.

During the next two periods, 17 and 18, all conditions were the same except that irradiated ergosterol was omitted. During these 6 days was obtained the greatest excretion of calcium and phosphorus observed at any time during the course of the investigation. This added output of calcium and phosphorus was entirely urinary. The value for urinary calcium rose from 0.403 gm. per 3-day period in the previous periods to 0.963 gm. per 3-day period during Periods 17 and 18. The corresponding phophorus value rose from 1.090 to 1.876 gm. On the other hand, the values for fecal calcium and phosphorus fell, in the case of the former from 0.034 to 0.027 gm. and of the latter from 0.309 to 0.262 gm. per 3-day period. The total calcium balance became −0.723 gm. per 3-day period and that of the phosphorus −0.311 gm. per 3-day period.

This marked increase in calcium and phosphorus excretion following the discontinuance of irradiated ergosterol is difficult to interpret. The increased excretion of these elements was in excess of that retained as a

result of ergosterol administration. This observation indicates that the effect of irradiated ergosterol was more pronounced in Periods 14 to 16 than was suspected from the comparison of the data obtained during these periods with those obtained during Periods 8 to 13.

The low average value of 0.027 gm. of calcium in the feces during Periods 17 and 18 may be taken to indicate a continuance of the ergosterol effect. The same thing may be stated regarding the corresponding values for phosphorus. This becomes evident when the values are tabulated, period by period.

TABLE 4.—TOTAL CALCIUM AND PHOSPHORUS BALANCE.

	Period 16.	Period 17.	Period 18.	Period 19.
Calcium:				
Urine	0.432	0.940	0.985	0.316
Feces	0.034	0.023	0.031	0.049
Total output	0.466	0.963	1.016	0.365
Intake	0.267	0.267	0.267	0.267
Balance	+0.199	+0.696	+0.745	+0.098
Phosphorus:				
Urine	1.079	1.936	1.815	1.464
Feces	0.320	0.235	0.289	0.318
Total output	1.399	2.171	2.104	1.782
Intake	1.827	1.827	1.827	1.827
Balance	+0.426	+0.344	+0.277	+0.450

Here it will be seen that although the fecal excretion of calcium was only 0.023 gm. during Period 17, it rose to 0.031 gm. in Period 18 and to 0.049 gm. in Period 19.

Periods 19 and 20 were control periods during which no medication was given. No comment is necessary other than to point out a tendency to return to the state which existed in the original control periods, 1 to 7.

During Periods 21 to 28 the diet employed was higher in calcium content and lower in phosphorus. This dietary change was made in order to determine whether or not less calcium would be retained if less phosphorus was given. One notes that during the first three periods on this diet the calcium balance was positive to the extent of +0.437 gm. and the phosphorus balance became negative (−0.556 gm.). Thus it will be seen that the additional calcium in the diet was entirely absorbed and retained. The resulting negative phosphorus balance was probably due to an inadequate phosphorus intake. *From these findings it is apparent that this individual was capable of retaining calcium other than in combination with phosphorus.*

The administration of ammonium chlorid in Periods 24 to 26 resulted in an increased calcium excretion, but was without effect on the phosphorus excretion. The calcium metabolism data suggest that *the ammonium chlorid acidosis prevented the retention of calcium and also mobilized calcium from the tissues (which had been retained previously) in some form other than calcium phosphate.* We are unable to state what this combination may have been. The failure to obtain an increase in the phosphorus excretion suggested that the ammonium chlorid therapy had been without effect on the phosphorus metabolism. However, the discontinuance of the drug during Periods 27 and 28 resulted in a marked diminution in the urinary phosphorus.

With the discontinuance of ammonium chlorid, in Periods 27 and 28 there resulted a return to the normal state for the dietary régime employed.

The nitrogen metabolism (Table 2) did not show noteworthy changes at any time. Except for Periods 8 to 13, during which the balance was −2.0 gm. per 3-day period, and Periods 17 to 18, during which it was −7.4 gm., all balances were positive, ranging from +0.8 to +5.4 gm. per 3-day period. The increased negative balance in Periods 17 to 18 probably explains some of the increased output of phosphorus during these periods.

It is noteworthy that throughout the period of study the patient did not appreciably lose weight. (Table 2.)

In Table 2 will be found the values for blood serum calcium and phosphorus. Throughout the period of study all values for calcium and phosphorus were normal except for the calcium value of 8.8 mg. per 100 cc. of serum on May 27, which coincides with the great loss of calcium from the body occurring at this time (Period 18). During the administration of irradiated ergosterol the serum calcium was unchanged; the serum phosphorus fell slightly and rose again after its discontinuance.

The acidosis obtained by ammonium chlorid was judged by determinations of the carbon dioxid combining power of the blood. At no determination was this found to be below 46.3 vols. per cent (on June 19).

Discussion. The occurrence of calcareous nodules in the subcutaneous tissues ("calcinosis universalis") is a rare condition affecting particularly children. Cases occurring in children have been reported by Langmead,[17] Verse,[18] Tisdall and Erb,[19] Morse[20] and Duret.[21] The last-named author observed the disease in a sister and brother. We have found no other reference in the literature which would suggest a familial tendency. The question of the etiology of the disorder has been discussed by each writer, but has remained unsolved. In the following summary, the results of the present study have been analyzed.

The possibility that this condition might be a disorder of uric acid metabolism seems unlikely because of the normal blood value and the negligible quantity of uric acid found in the biopsy specimen.

There is very little to point to a gross disturbance of cholesterol or fat metabolism. The blood cholesterol was normal. The cholesterol and fatty acid content of the biopsied specimen was not more than one might expect.

Further analysis of the calcareous material showed it to be composed of calcium carbonate and calcium phosphate in proportions essentially the same as that of normal bone and pathologic calcifications found elsewhere.

Our histologic study was limited to the subcutaneous nodules easily accessible for biopsy. This examination did not reveal any adequate explanation of the calcifying process. There was no evidence of any of the usual abnormalities which are known to cause pathologic calcification, namely: chronic inflammation, infarction, hemorrhage or tissue necrosis. The earliest abnormality noted was the deposition of finely divided calcium particles around the periphery of fat cells, which otherwise histologically appeared to be normal. No evidence of "calcium binding substances within degenerated areas"[22] was seen, since calcification appeared in areas of fat before there was any microscopic evidence of degeneration. The calcium when first retained may have combined with fatty acids, but if so did not remain in this form, as the analysis of one of these deposits showed that all the calcium could be accounted for as calcium carbonate or tertiary calcium phosphate.

The disease process appeared from the histologic standpoint to have progressed until calcium had been deposited within fat cells and eventually replaced whole fat lobules. Once formed, these larger lime deposits became foreign bodies, stimulated fibrosis, caused formation of giant cells and slight lymphoid cell infiltration. Many nodules had coalesced into large masses, some had broken down and partially extruded their contents. Where this had occurred cicatrices had formed. We think that the presence of occasional hyalinized, thick-walled arteries was not an important etiologic factor. It is more probable that these vascular changes were secondary to the calcification and accompanying fibrosis. We agree with the conclusion of others[19] that inflammatory changes are not causative factors in these deposits.

Verse[18] studied and reported this disease process in a boy, aged 15 years, together with the postmortem findings. In addition to the subcutaneous calcareous nodules, he found that lime salts had been deposited in the interstitial connective tissue of muscle and in the connective tissue around muscle bellies, tendons and nerves. Calcification about the capsules of mesenteric lymph nodes was also observed. Otherwise there was no calcification of the internal visceræ. From histologic study he thought that the calcium salts had been deposited in living connective tissue. As indicated by Roentgen ray examination, the present case also had marked calcification of the muscles of the arms and legs.

While we could find no microscopic evidence of previous tissue injury, it seemed important that this obscure process involved the regions of the body which are liable to trauma and are most subject to muscular activity. As previously noted, the more protected portions of the body, the thorax and abdomen were particularly spared.

Metabolic studies showed that this patient had an extraordinary ability to retain the absorbed calcium and phosphorus. This tendency was more marked in the case of calcium than phosphorus as demonstrated by the low fecal and urinary values for the former. Regardless of the calcium content of the diet or medication, the fecal calcium values remained extremely low, never exceeding 49 mg. per 3-day period. It seems fair to assume that a higher calcium intake would not have increased the fecal calcium values. Urinary calcium values as low as those observed during the control periods (1 to 7) are usually associated with a lowered serum calcium.[23] In the present case the low urinary calcium values were undoubtedly due to the marked affinity of the body tissues for calcium, thus resulting in a marked retention of this element. There was no evidence of increased calcium and phosphorus retention in the bones that could be demonstrated by roentgenograms. *The results obtained during Periods 24 to 25 suggest that when calcium is first*

FIG. 1.—Posterior view of patient showing numerous lesions in all stages of development over the buttocks and posterior aspects of the arms and legs.

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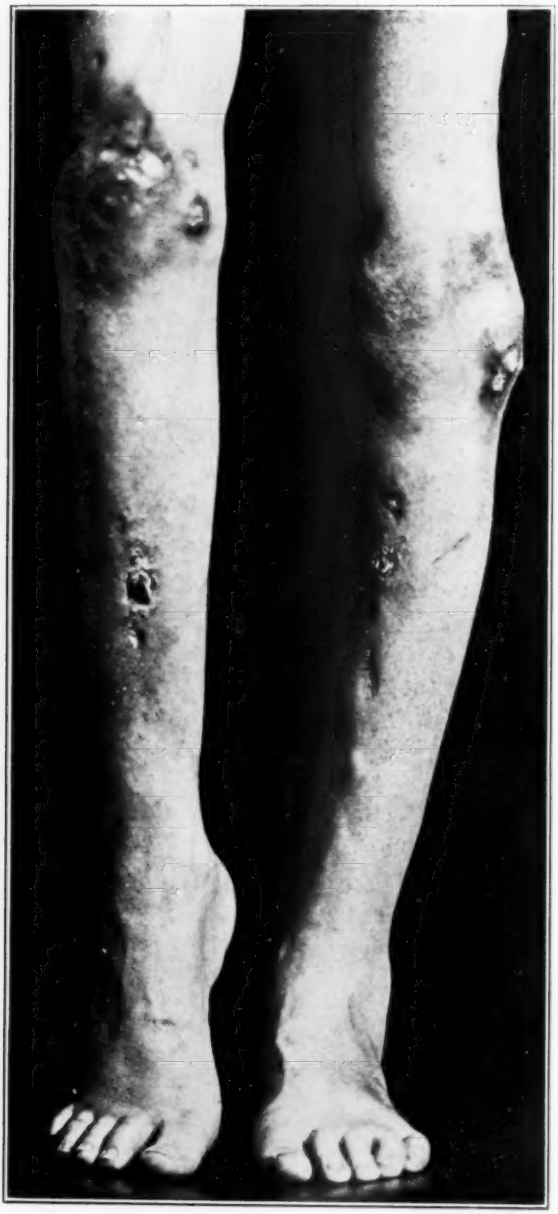

FIG. 2.—Anterior view of the legs. All types of lesions are seen. They are most numerous in the region of the knees.

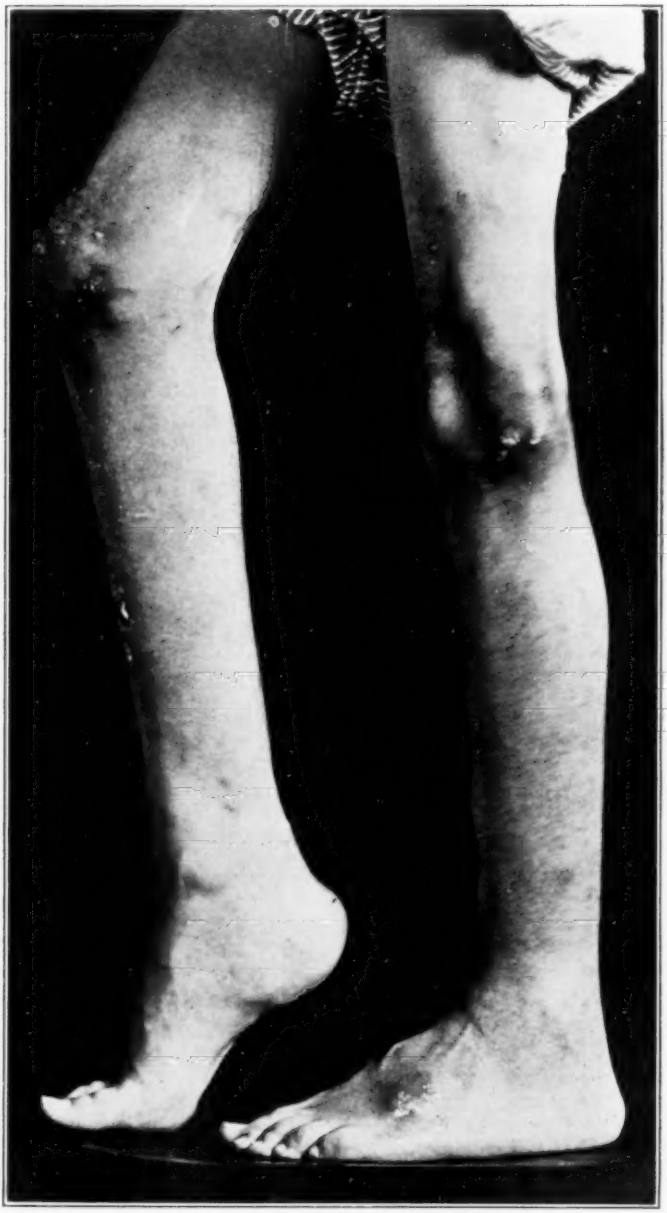

FIG. 3.—Side view of the legs, showing flexion deformity of the right leg. The nodules on the outer aspect of the left knee have become infected.

FIG. 4.—Roentgenograms of the arms showing the marked deposition of calcium in the subcutaneous tissue of the right forearm and the sheaths of the extensor muscles of the left forearm.

FIG. 5.—Roentgenograms of both thighs. The subcutaneous calcium deposits are well demonstrated. The ham-string muscles of the right leg show depositions of calcium in the sheaths surrounding them. This is seen to an even greater extent in the sartorius muscle.

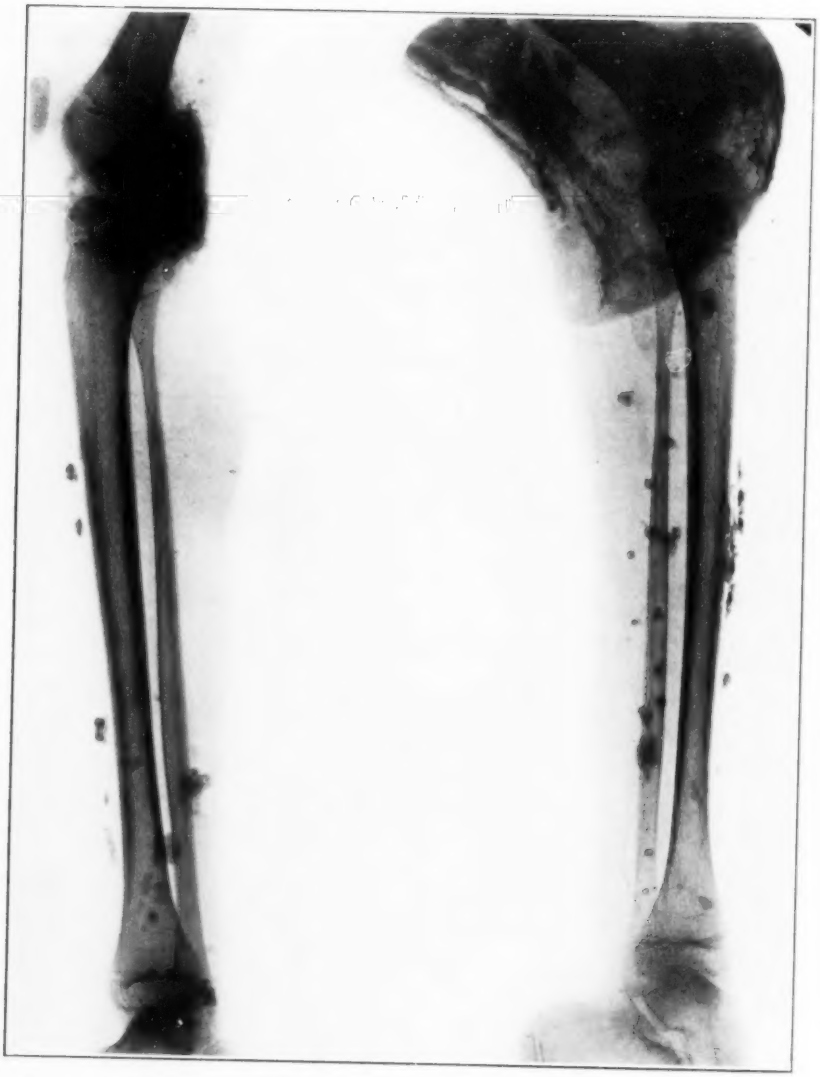

FIG. 6.—Roentgenograms of both legs. Calcium deposition in the subcutaneous tissues and muscle sheaths is easily seen.

FIG. 7.—Roentgenograms of both knees, illustrating the extensive calcium deposits in the region of both knees.

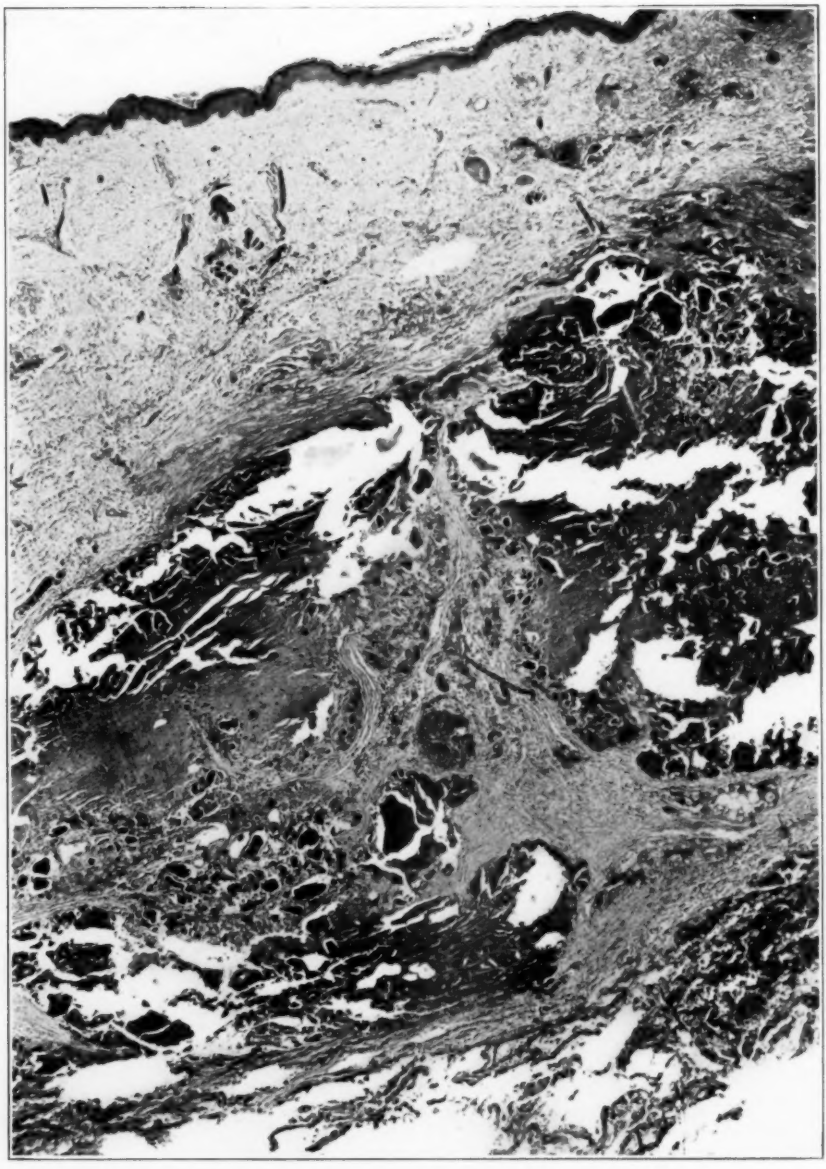

FIG. 8.—A photomicrograph with very low magnification showing a larger area of calcification in the subcutaneous tissue. Section was stained with hematoxylin and eosin. ×28.

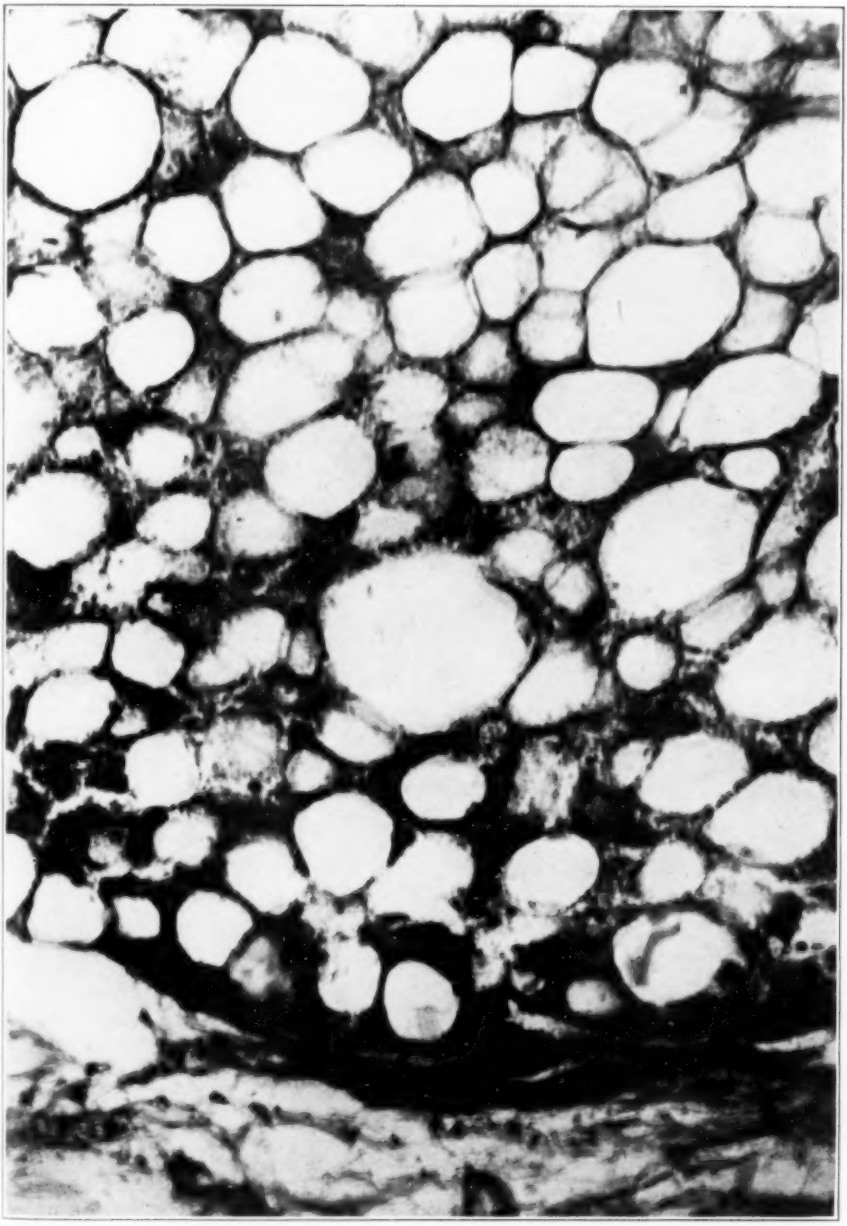

FIG. 9.—A photomicrograph (×300) to illustrate what appeared to be the initial lesion, namely: a deposition of calcium particles about the periphery of intact fat cells.

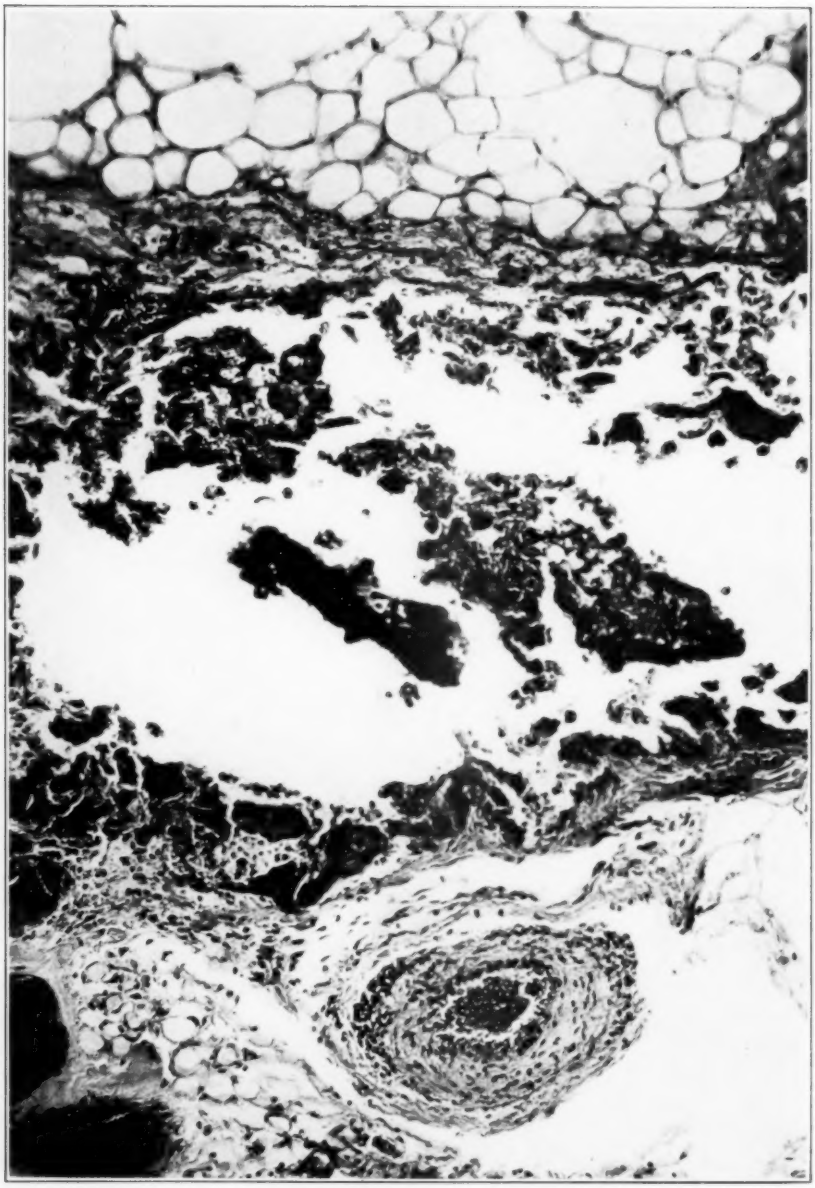

FIG. 10.—An artery with thickened and hyalinized media in the proximity of a calcified area. Section stained with hematoxylin and eosin. ×160.

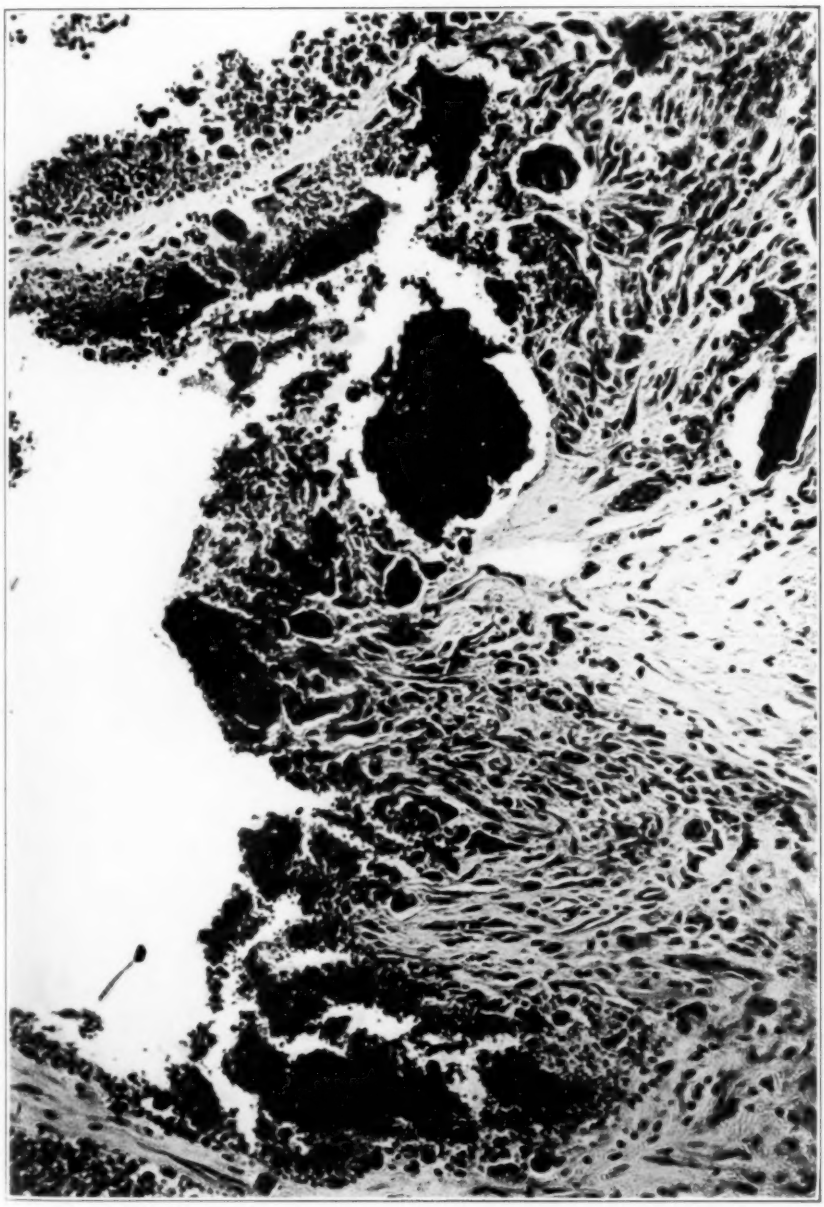

FIG. 11.—Early connective-tissue proliferation and giant-cell formation in response to calcium deposit in fat. ×160.

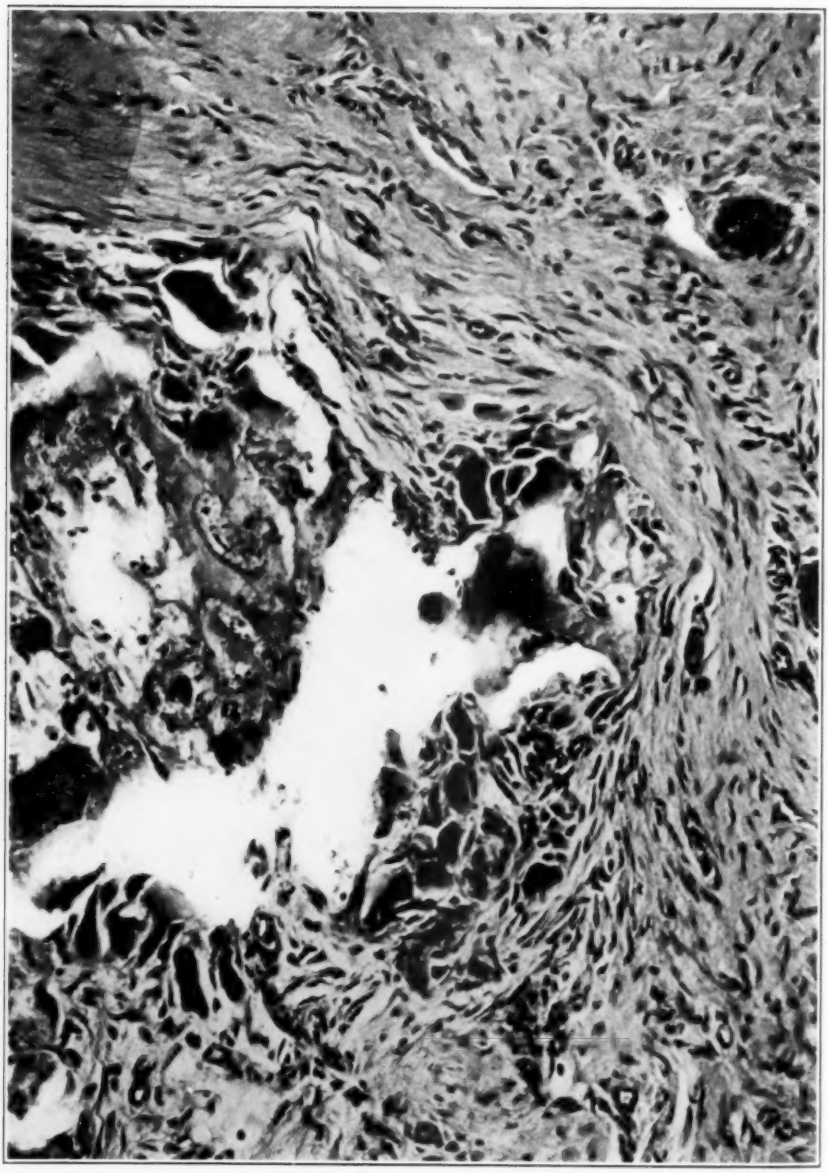

FIG. 12.—A photomicrograph (×210) showing fibrosis and foreign-body giant-cell reaction about an area of calcification. Section stained with hematoxylin and eosin.

deposited it does not necessarily have to be accompanied by phosphorus.

We are unable to offer any explanation as to why this individual retained calcium and phosphorus to this degree. Irradiated ergosterol poisoning and parathormone overdosage are known to cause metastatic calcification, but this individual had no signs or symptoms which would justify such a diagnosis.[24,25,26,27] Furthermore, the calcification seen in the last-mentioned conditions occurs regularly in the kidneys, stomach, lungs, heart and bloodvessels; these organs were not involved in either our case or the one described by Verse.

As a result of the above considerations it seems fair to conclude that calcium and phosphorus metabolism is abnormal in these rare cases of calcification of the subcutaneous tissue. This is well shown by the excessive retention of calcium and phosphorus. The increased retention was evidently due to an unusual affinity of certain tissues for these elements. We are unable to state what intracellular changes, unrecognizable microscopically, preceded the deposition of calcium in these regions.

The belief that this condition is due in part to a general metabolic disturbance is contrary to the views of Tisdall and Erb[19] and of Wilens and Derby.[1] They reasoned that the normal blood values for calcium and phosphorus argued against a metabolic disorder. However, this view seems scarcely tenable in the light of the calcium and phosphorus balance studies presented. The observed metabolic disturbance serves well to emphasize again that study of the serum calcium alone "merely shows the height of the 'calcium stream' but gives no indication as to its direction of flow."[14]

From our studies we would suggest the following treatment: the use of a diet inadequate in calcium in conjunction with a decalcifying agent, such as ammonium chlorid. However, the employment of such therapy over a long period of time might be expected to result in marked skeletal decalcification as well. The prognosis is at best, unfavorable.

Summary. 1. Further studies in a case of "calcinosis universalis" are reported.

2. Calcium and phosphorus balance studies indicated a marked tendency to retain the absorbed calcium and phosphorus in spite of normal blood calcium and phosphorus values. This tendency was more marked in the case of calcium than phosphorus.

3. Ammonium chlorid acidosis produced an increase in the urinary excretion of calcium and phosphorus.

4. Chemical analysis of a calcareous nodule removed at biopsy showed the presence of a negligible quantity of uric acid, a moderate amount of cholesterol and fatty acids, and calcium and phosphorus in the amount and ratio, one to the other, commonly found in adult bone and pathologic human calcification.

5. Histologic study showed no evidence of antecedent tissue necrosis, nor did it suggest any explanation for the abnormal calcium deposits.

6. The above results suggest that the basis of the disorder lies in an abnormality of calcium and phosphorus metabolism. It is suggested that the increased retention of calcium and phosphorus may be the result of local cellular conditions as yet undetermined.

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TOXOID AS AN IMMUNIZING AGENT IN DIPHTHERIA.

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The value of diphtheria toxoid in the active immunization of children against diphtheria is now well established. Reports on its use in over 1,000,000 cases demonstrate that it is an efficient and safe product to use.[1] Toxoid has enjoyed considerable popularity in France and in Canada, but its use in this country has been relatively limited. It is the purpose of this report to give the results obtained with toxoid in a controlled group of 358 children.

Procedure. Toxoid Used. The material employed in this study was a standardized commercial product.[2] It is prepared[3] by growing a virulent strain of diphtheria bacillus in broth which does not contain horse meat. This is to eliminate the possibility of sensitization to horse protein. At the end of a week this material is filtered and tested for its toxic value. Federal regulation requires that the toxin from which toxoid is made shall have an L+ (lethal) dose of not over 0.2 cc. or a minimal lethal dose of not more than 0.0025 cc. The "Lf" value, in other words, the amount of toxin in cubic centimeters which is required to flocculate 1 unit of antitoxin, or its reciprocal, the antigenic value, and the "Kf" value (flocculation time) are then determined. No toxin is used which requires more than 0.1 cc. to flocculate 1 unit of antitoxin. Such a toxin has 10 immunizing units, according to the French standard. After the toxin is selected a small amount of U. S. P. formalin is added to bring about complete detoxification in a reasonable period of time. This amount must not exceed 0.4 per cent. The formalized toxin is kept at a temperature of 39° C. At weekly intervals intradermal tests are made on guinea pigs to determine the rate of its detoxification. When it is believed that this has progressed sufficiently far the material is removed to the refrigerator and 5-cc.

portions are injected into a series of 300-gm. guinea pigs. When detoxification is completed no effect should be noted in the guinea pigs over a period of 30 days. The material is ready when 10 pigs injected with 5 cc. each show no signs of diphtheria poisoning at any time during a period of 30 days. The time required for complete detoxification will vary with each lot of toxin. The minimum antigenic requirements are that at least 10 guinea pigs, weighing 270 to 320 gm., shall receive subcutaneously the initial human dose. At the expiration of six weeks each of these pigs is injected subcutaneously with 5 minimal lethal doses of a stable diphtheria toxin. At least 80 per cent of these animals must survive for 10 days. The flocculation value of the finished product is then again determined, and if there has been any loss in flocculation value the product is discarded. The toxoid contains approximately 50 times the amount of media and bacterial protein that is present in the toxin-antitoxin mixture. The fact that toxoid is resistant to heat, retains its antigenic power, is nontoxic and free from horse serum makes it a most desirable preparation.

This study was carried out in the Children's Outpatient Department of the University of California Hospital, where they request that every well baby and child over 6 months of age be given a routine Schick test. To obviate errors in the technique of testing, the Schick testing is done one afternoon a week by a house officer who is on service for 6 months at a time. A fresh solution of Schick and control material is used each testing day. The Schick tests are read in 72 hours, and if positive the toxoid is then given in two doses of 1 cc. each, at an interval of 10 days. Re-Schick tests with controls are performed 3 months after the completion of the course of toxoid injections, and these re-Schick tests are read in most instances by the same man who administered and read the original Schick test. Every care is exercised in the performance of the Schick test and its readings, as these are the major sources of error.[4]

TABLE 1.—AGE OF PATIENTS TREATED.

Age.	Number.
3 mos.	3
5 "	4
6 "	12
7 to 12 "	46
1 to 3 yrs.	94
3 to 5 "	56
5 to 10 "	74
10 to 15 "	23
Total	312

RESULTS. This study comprises data on 358 Schick-positive city children, between the ages of 3 months and 15 years. (Table 1.) Of these children 333 received two injections of 1 cc. each of toxoid at an interval of 10 days. Twenty-five children received only one

injection. Of the group receiving a total of 2 cc. of toxoid 327 (98 per cent) were Schick negative after a period of 3 months or more. Of the group receiving a total of 1 cc. 21 (84 per cent) were rendered Schick negative on retests. (Table 2.) These results correspond well with those found in other reports. (Table 3.) Our experience, as well as that of Weinfeld and Cooperstock,[5] would indicate that two injections of 1 cc. each of toxoid are as effective as 2 cc. given in three doses. It has the added advantage

TABLE 2.—RESULTS WITH TOXOID.

		Negative after toxoid.	
	Total No.	No.	Per cent.
Positive Schick tests	358	348	97
2 cc. toxoid	333	327	98
1 cc. toxoid	25	21	84

TABLE 3.—COMPARATIVE STUDIES IN IMMUNIZATION WITH TOXOID.

Author.	No. of cases.	Dose, cc.	No. of injections.	Interval.	Per cent immunized.
Harvier and Requin[8]	88	0.5 1.0	2	3 weeks	95
Ramon and Helie[1]	..	0.5 1.0	2	3 "	90 to 95
		0.5 1.0 1.5	3	3 "	97 to 100
Moloney and Frazer[6]	66	0.5 0.5	2	1 month	70
Zingher[14]	100	0.5 0.5 1.0	3	2 weeks	98
		0.5 0.5	2	...	86
		0.5	1	...	60
Roubinovitch, Loiseau and Laffaille[12]	130 53	0.5 0.5 1.0	1 2	... 3 "	37 81
	79	0.5 1.0 1.5	3	3 "	88
Bloomberg and Fleming[9]	208	0.5 0.5	2	1 month	68
	38	0.5 1.0	2	1 "	84
	32	0.5 1.0 1.0	3	1 "	94
Schwartz and Janney[11]	128	0.5 1.0 1.0	3	3 weeks	98
Weinfeld and Cooperstock[5]	89	1.0 1.0	2	3 "	92
	15	1.0	1	...	46
Dick and Dick[13]	100	0.5 1.0 1.5	3	2 "	94
Author	333	1.0 1.0	2	10 days	98
	25	1.0	1	...	84

of saving time and also the pain of one injection. Results given in Table 3 suggest that when a total of 2 cc. of toxoid has been given one may expect from 90 to 98 per cent negative Schicks on retesting. When 1 cc. only is given the percentage will be below 90 per cent. Toxoid has not been in use for a sufficient period of time to determine the length of the immunity produced. Three cases of this series were retested after an interval of 3 years and found to be Schick negative. (Table 4.)

TABLE 4.—RESULTS OF SHICK RE-TESTS AFTER TOXOID.

	No. Schick retested.	No. Schick negative.	Per cent negative.
Total number of children Schick retested	358	348	97
At 3 months	205	195	95
At 4 "	90	90	100
At 5 "	28	28	100
At 6 "	17	17	100
At 6 " to 1 year	15	15	100
At 3 years	3	3	100

REACTIONS. Both local and general reactions are seen with toxoid as with the toxin-antitoxin mixture. The reactions may occur after the first, second or third injection of toxoid. Weinfeld and Cooperstock[5] state that local reactions are rare and general reactions are never seen in children under 7 years of age. Maloney[6] and Frazer believe that reactions are very rare in children under 8 years, while local reactions occur in about 25 per cent of children over 8 years of age. Ramon[1] finds that reactions are rare under 8 to 10 years, and suggests that they occur principally in those children with a pseudo-Schick reaction. He says from 20 to 40 per cent of persons over 10 years have slight reactions; from 10 to 15 per cent have fair reactions and from 1 to 5 per cent strong reactions. Fitz-Gerald[7] summarized an experience with 10,600 preschool children and says that 2 to 3 per cent had fairly marked reactions and 25 per cent had slight local reactions. Harvier and Requin,[8] in a group of 235 children, observed feeble reaction in 21 and general reactions in 35.

In a study of 278 children Bloomberg and Fleming[9] saw no reactions in children under 6 years of age either from the 0.5-cc. or the 1-cc. dose. Ramon[1] has collected data on over 1,000,000 injections of toxoid and has not found a serious accident or fatality.

The reactions produced by toxoid are probably due to the fact that it contains a relatively large amount of media and bacterial protein. It is thought by some workers[1,5] that persons who react to toxoid have been sensitized in some way to these specific proteins or that the reactions may be considered as nonspecific protein reactions. This would account for the reactions occurring so rarely in younger children and so readily in those persons showing a pseudo-Schick reaction. Moloney[10] has shown that those persons who react to toxoid are more readily immunized than nonreactors.

Two cases in this series who had general reactions were immunized by 1 cc. of toxoid given in one dose.

In Table 5 we have listed the children who gave general reaction together with a note as to a history of allergy in these cases. J. F. is an exceptionally young child to react to toxoid, being only 5 years of age. T. D. was given toxoid and in 3 hours developed such a severe asthmatic attack as to necessitate hospitalization.

TABLE 5.—GENERAL REACTIONS FROM TOXOID.

Case.	Age, yrs.	Sex.	Reaction.	Allergy.	No. of injections.	Repeated Schick.
J. F.	5	M	General	No	1	Negative.
W. C.	7	M	General	No	2	Negative.
T. D.	10	F	General	Asthma	1	Negative.

Three patients in this series had general reactions. These came on within 8 hours and lasted for about 24 hours. About the site of injection a large area of redness developed, which was tender and painful to touch, and caused some discomfort in movement of the arm. General symptoms were anorexia, malaise, nausea, headache and marked irritability, with some slight rise in temperature. In 1 of these cases a typical asthmatic attack was precipitated by an injection of toxoid. It has been suggested by Weinfeld and Cooperstock[5] that persons with an allergic background may react to toxoid more readily than those without such a history. In a group of college students they found that of those persons with an allergic history 40 per cent gave reactions to toxoid as against 16 per cent in those without an allergic back ground.

Schwartz and Janney[11] feel that allergy does not play such a prominent rôle in preschool children, as in their study of 128 children there was only 1 reaction. Their series included 14 cases of eczema, 15 of seborrheic dermatitis and 1 each of asthmatic bronchitis and hay fever. They are, therefore, of the opinion that an allergic makeup does not necessarily provoke a toxoid reaction in a preschool child.

A review of all the cases of allergy in our clinic was made, and 7 patients were found who had received toxoid. Of this number only 1 had a reaction. While this is too small a group from which to draw conclusions, it suggests that in children, age and the chance for acquired sensitivity are of equal or more importance than allergy in the production of reactions. Children under 8 years react much less frequently than those over this age.

The difference in the number of reactions reported by various workers may possibly be explained by the difference in the toxoid used. The earlier preparations gave more reactions. The present methods of preparation and refinement with the resulting minimal amounts of culture and media protein give fewer reactions. Local reactions in this series were so slight that in no case did we have anyone who objected to the second dose of toxoid being given.

Summary. The use of toxoid in the active immunization of 358 children against diphtheria is reported; 333 children received 2 cc. of toxoid and 98 per cent were rendered Schick negative; 25 received only 1 cc. of toxoid and 84 per cent were immunized. In this series toxoid was given in two injections of 1 cc. each at an interval of 10 days. This routine was found to give satisfactory results.

Both local and general reactions are seen with toxoid. Age, the possibilities of sensitization to the protein of the Klebs-Loeffler bacillus or the media proteins and a background of allergy are all factors concerned with the production of reactions. Children under 8 years react much less frequently than children over 8 years of age.

From our own observation and on evidence in the literature, one may expect from 90 to 98 per cent negative Schick reactions after a total of 2 cc. of toxoid has been given. When a total of 1 cc. only is given the number of Schick negative results will usually be below 90 per cent.

Conclusion. Toxoid is a safe, reliable and efficient preparation to use in the immunization of children against diphtheria.

The author wishes to acknowledge the generous supply of toxoid which was furnished through the courtesy of Dr. J. G. Fitz-Gerald, Connaught Laboratories, University of Toronto, Toronto, Canada, at the initiation of these studies. Thanks are also due Dr. Robert Cutter, Cutter Laboratory, Berkeley, Calif., for his interest in the development of toxoid and for his many suggestions during the course of this study.

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TOXICITY AND RATE OF ELIMINATION OF ORGANIC ARSENICALS (STOVARSOL AND TREPARSOL) IN THE TREATMENT OF ENDAMEBIASIS.*

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The convenient method of treating endamebiasis by the oral administration of organic arsenicals has led to more or less indiscriminate use of these drugs. In view of the vast amount of experience that has been derived from the use of arsphenamin, it is difficult to understand the free and easy manner in which stovarsol and treparsol have been used. A review of the reported complications in the use of these drugs convinces us of two facts: (1) That the drugs are continued in spite of warnings of intolerance, and (2) that certain persons are very sensitive to arsenic in any form.

There are numerous reports of toxic erythema and even exfoliative dermatitis from the use of the two drugs. In most cases the cutaneous reaction is manifest after only small or moderate amounts of arsenic have been taken. Dargein and Doré reported a death from treparsol. Their patient was an elderly man, with active syphilis of the central nervous system. Treatment was begun with the arsenical and although the dosage was moderate, yet an acute break occurred and the patient died in coma. This resembles the danger of the use of arsphenamin in syphilis of the central nervous system. They considered the death as due to a Herxheimer reaction. Milan and Garnier reported a death from treparsol as the result of administering treparsol to a young woman with syphilis. She was given 4 tablets (1 gm.) daily for 9 days, when delirium developed and she died in 24 hours. The dose in this case was greater and the treatment more prolonged than we have used for endamebiasis. May reported the first death from treparsol. In this case the patient began to show signs of intolerance to arsenic, but she continued using the drug, and in 2 days became unconscious and died in coma. La Terza, in 1930, reported experiences from Brazil, with treparsol, namely, 2 cases with 2 deaths.

In the literature we were able to find records of only 2 deaths attributed to stovarsol poisoning (Willner and Meleny). Porot

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reported on sensory disorders and pseudotabes due to stovarsol. In 2 cases stovarsol had been used intermittently over a period of months in an endeavor to eradicate *Giardia lamblia*. The symptoms of involvement of the central nervous system came on insidiously, beginning with rheumatic pains, and continuing until there was marked disability. The third patient had taken 0.25 gm. stovarsol daily for 10 days because of amebic colitis. Shortly after the conclusion of this one course, peripheral neuritis was manifested. Further reference to this complication was not found. We have observed 1 severe and 1 mild case of peripheral neuritis following the ingestion of stovarsol but none from treparsol.

In the first case acute amebic colitis had been controlled by 3.5 gm. of stovarsol. The patient was dismissed from observation, and two additional courses were prescribed, with 10-day intervals between courses. A few weeks after the last course bowel symptoms recurred and a fourth course was taken without our knowledge. The patient did not respond well; the dysentery was not as completely controlled, and aching appeared in the legs. He decided to take a fifth course. Following this severe symptoms of peripheral neuritis developed, which totally incapacitated him. The neuritis persisted for months. The urine was examined for arsenic 3 months after the last stovarsol was taken. Arsenic in appreciable quantities was found. The colitis itself apparently was cured by yatren; this was confirmed several months later.

In the second case the patient had amebic colitis. He received 7.5 gm. of stovarsol in two courses. Fifty days after the last course arsenic was found in the urine. The mild neuritis which had developed subsided in a short time. Toxic erythema developed after the first course, but cutaneous reaction did not occur after the second course.

In both these cases warning signs were put out. The first patient might not have escaped neuritis, but failure to control the colitis with three courses of stovarsol should suggest a change of treatment. In the second case the cutaneous reaction warned of questionable tolerance to arsenic.

To emphasize the individual factor in such a reaction, it may be noted that we examined the urine of another patient 13 days after the completion of a course, consisting of 3.75 gm. of stovarsol. Arsenic was not present in the specimen.

In our experience with these two arsenicals there have been no deaths. Two cases of peripheral neuritis have been noted. We also have data concerning six cutaneous reactions in 123 cases in which treparsol was used and of four cutaneous reactions in 130 cases in which stovarsol had been used during the last 4½ years. In 9 of the 10 cases toxic erythema occurred, which subsided in 3 to 5 days. In the tenth case there was enough cutaneous reaction to prompt the diagnosis of exfoliative dermatitis. This patient

recovered in a week and did not suffer further ill effects. The percentage of cutaneous reactions with treparsol (4.8 per cent) is somewhat higher than with stovarsol (3 per cent). We have prescribed these arsenicals for many other patients, but data are available only concerning the 253, all of whom received from 3.5 to 16 gm. of the drugs.

The 2 cases of peripheral neuritis developing subsequent to the use of stovarsol prompted us to consider the rate and channel of elimination of the arsenic of this drug. Accordingly, the urine and feces were collected for a period of 7 days from 5 patients who had received 3.5 gm. or more of stovarsol. Attempts to determine quantitatively the arsenic excretion by the ordinary Gutzeit procedure were unsuccessful, however. Except for the fact that qualitatively it was found that arsenic was still being excreted in the urine at the end of 7 days, the experiment did not furnish the information which we desired, namely, the ratio of urinary excretion to fecal excretion.

Following the development by one of us (Osterberg) of the electrolytic Gutzeit procedure for the estimation of arsenic, it was decided to conduct similar elimination studies following the administration of treparsol, since our interest has been focussed on this drug.

Four patients of the group receiving treparsol were selected for observation. A single course of treatment consisted of the daily ingestion of 0.75 gm. of treparsol for 4 days. It was felt that the degree of absorption of the drug from the intestinal tract was dependent on the physical dispersion; hence, it would seem the more desirable to use the compound in the form of a finely ground powder rather than as a tablet, as it is commonly dispersed.

However, in order more closely to simulate the actual conditions of treatment with this drug as it is commonly practised, it was decided to request 2 of the patients to swallow the entire tablet without chewing and the remaining 2 patients to chew the drug thoroughly before swallowing.

From the results of the determinations by the electrolytic Gutzeit method, it was found that the major portion of the arsenic is eliminated in the feces. When the treparsol tablets were swallowed without chewing the ratio of arsenic in the urine to that in the feces was 1 to 9 and 1 to 16. In the cases in which the tablets are thoroughly chewed the ratio of arsenic in the urine to that in the feces was 1 to 3.

In all cases 90 per cent or more of the total arsenic was recovered by the third day following the last ingestion. The absolute amount and the relatively greater proportion of arsenic in the urine in the cases in which chewing of the drug was resorted to indicate that the physical condition of the drug is of prime importance in its absorption. The amount of arsenic remaining in the feces repre-

sents unabsorbed treparsol rather than arsenic excreted by this route.

Realizing that individual variations to arsenic exist, we hesitate to postulate that treparsol, used in doses of 0.25 gm., two to three times a day, with a total amount of the drug not to exceed 3 gm., is preferable to stovarsol solely because, as we have shown in the study of elimination of arsenic under treparsol treatment, the arsenic was eliminated in a period of 7 days and also that peripheral neuritis did not result, whereas if patients were under stovarsol treatment arsenic was present weeks and even months after discontinuing treatment, and peripheral neuritis was encountered as a complication. However, we consider that since the cutaneous reactions occur in about an equal percentage, and as we have not known of peripheral neuritis to occur after the use of treparsol, the clinical experience seems to bear out the study of elimination in favor of treparsol.

Chen, Anderson and Leake have recently reported on the rate of urinary excretion of stovarsol and carbarsone. In 1 case 2.75 gm. of stovarsol was administered in 6 days, and in the second case 3.5 gm. was administered in 7 days. In the former, 29 per cent of the arsenic administered was recovered from the urine in 14 days after treatment was begun; in the latter, 17 per cent was recovered in 10 days. These observations indicate the persistence of arsenic in the urine; however, the amount remaining is uncertain as data relative to the arsenic excreted through the bowel was not obtained.

SUMMARY OF RESULTS.

Arsenic eliminated, mg.			Ratio $\frac{\text{Arsenic in urine}}{\text{Arsenic in feces}}$
Urine.	Feces.	Total.	
192	595	787	1 to 3 treparsol chewed.
184	546	730	1 to 3 treparsol chewed.
45	741	786	1 to 16 treparsol not chewed.
70	645	715	1 to 9 treparsol not chewed.

Conclusion. New remedies are constantly being sought in the treatment of endamebiasis. It is possible that nonarsenical remedies, such as anayodin (yatren), or more recently dihydranol, will supplant the arsenical drugs. Emetin will continue to prove a bulwark for controlling the acute phase of the disease, but we feel that it must be used in conjunction with other preparations to effect cure in a large percentage of cases. We have found emetin and treparsol very satisfactory; they constitute the first line of defense unless there are contraindications to their use. Arsenic has proved to be such an effective parasiticide that it will probably continue to be used, although a less toxic arsenical preparation may be developed.

The rate and route of elimination of arsenic following the administration of treparsol has been determined in 4 cases selected from a group of 253, in which the patients were suffering from endamebiasis.

The fineness of the ingested drug determines to a large degree the extent of its absorption and the ratio of arsenic in the urine to that in the feces.

Our data tend to show that treparsol is more rapidly eliminated than stovarsol and that the possibility of untoward sequelæ developing is lessened with the former drug.

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GUIDES TO THE PREVENTION AND TREATMENT OF THE SIMPLER NEUROSES.

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In this day of overspecialization the internist holds a rather unique position in medicine. He alone is privileged to consider his patient as a whole; to investigate without prejudice not only the body but the mind; and if an explanation for symptoms be not found after appropriate physical examinations, to seek their cause in the patient's relation to his environment. If he does not exercise this prerogative, a valuable opportunity has been not only neglected, but more often irreparably lost. The patient who leaves his doctor's office with psychogenic symptoms unrecognized travels thereafter like a derelict from one specialist to another, and often finally reaches the charlatan, who at least takes the symptoms at face value and offers hope of cure.

Why does the internist so often fail to accept his responsibility and make no adequate study of his patient's emotional life? I believe there are two reasons. In the first place most internists

believe that all cases of neurosis demand a great many hours of treatment, and that neither he nor the patient can afford the time; secondly, he often does not know what to say, how to get at the facts or what to do about them if discovered.

With full recognition that prolonged treatment is essential in many cases, it is my belief that a very large proportion of these patients both can and must be helped by the internist if they are to be helped at all. Complete cure, which would imply entire self-understanding, certainly is often not attained. But relief from symptoms will result in numerous patients, after a very few hours' work. Even if entire relief be not secured, the subject of psychotherapy is opened up. The patient at least partially understands his problem and may accept a suggestion that he continue further with a psychiatrist the work already begun.

The physician's greatest stumbling block is lack of thorough psychiatric training. This defect in medical education is not insuperable. The internist cannot undertake a complete psychoanalysis, but he should be able to understand the various types of difficulties frequently underlying neurotic symptoms, and should have a practical knowledge of the simpler methods of therapy.

At the outset both the patient and physician must be convinced that organic disease does not exist, or if it be present, that it cannot wholly explain the symptoms. The patient, moreover, must be made to feel that his physician believes his symptoms to be real, as they are; not imaginary as they so frequently are labelled even today. Lastly, the physician must be able to explain how real symptoms can occur in the absence of organic disease, and must uncover, if he can, the sufficient cause for symptoms in his patient's unconscious emotional life.

It is usually wise with such cases to begin by describing the physiologic changes popularly known to be associated with emotional tension; the dilatation of skin arterioles and capillaries caused by shame and the constriction caused by fear. Many patients have experienced frequency of urination or diarrhea in relation to nervous tension, or loss of appetite and nausea preceding an after-dinner speech or dramatic performance. It is emphasized that the diarrhea or nausea are as real under these circumstances as diarrhea or nausea accompanying dietary indiscretion or disease of colon or stomach. It may be valuable to illustrate the changes in function accompanying emotional disturbance by quoting Cannon's experiment with the cat, in which under Roentgen ray the normal gastric peristalsis was seen to cease when a dog was brought into the room.

The patient is thus convinced not only that he and his symptoms are being taken seriously, but that varied symptoms may be caused by emotional strain, notably by fear. At this point he may seize the opportunity to volunteer an explanation of his own symp-

toms; and although this attempt is usually abortive, at times a superficial neurosis may thus be entirely resolved, the patient saying that he "knows what is the matter with him," and then pouring out a story of worry or fear. Sometimes the unrecognized fear of a specific disease (often cancer) will be brought to light, the patient for the first time daring to meet this fear in the open and ask his physician for the truth.

If the problem is not solved at this point, and it usually is not, I find it wise to take time to review for the patient various types of emotional difficulty which occur in human beings, and to explain how symptoms may result from them.

In the World war we were all familiar with physiologic disturbances in otherwise normal organs. For instance, certain soldiers complained of precordial pain, dyspnea and rapid heart action, all symptoms of heart failure, yet when the heart was examined it was found to be without disease. It is interesting that the symptoms for the most part developed not at the front, and not in deserters, or men retired because of injury, but in those men behind the lines who had to look forward to a return into danger. Such a man was faced with two alternatives: either he must expose himself to injury or lose his self-esteem. Faced with this dilemma, a coward might flee, achieve safety and suffer no neurosis; or a particularly brave man return to duty in spite of fear; but for many neither alternative was possible. The inevitable unconscious conflict resulted in bodily symptoms, whereupon a third alternative became apparent: to escape peril without loss of self-esteem through symptoms. The various symptoms resulting from the soldier's conflict became the means of saving his most precious possessions, life and self-esteem. What wonder the symptoms were unconsciously embraced and retained!

Many neuroses in civil life follow a similar causative pattern. Life appears overdangerous. Go forward we must, but to go forward and retain self-esteem appears to the subconscious mind too difficult. The consequent impasse results in physical symptoms, and the symptoms are again unconsciously welcomed as a solution of the problem. Is it not our duty as physicians to discover why such patients have grown to fear life, and to prove to them that the danger sensed exists not of necessity, but because of a mistaken point of view, usually the result of bad training in infancy and childhood?

The child's early training even today is often unfortunate. Children are either made too much of, or neglected and discouraged at the outset. In either case they very early develop a disproportionate desire for power. The child who is made the center of attention soon begins to enjoy this central position above all else, and will make every effort to hold it. Misbehavior in early childhood often enables him to focus upon himself the attention of

which he feels in need. He may refuse to eat, or defecate. He may have tantrums. Whatever causes evident consternation to his parents is grist to his little mill. When such a child first enters school he is unhappy. He misses his home where he was a central figure and, symptoms coming to the rescue, he often succeeds in regaining this friendly country. People speak of him as being "too sensitive" for school. Such a child will be shy, will take responsibilities overhard. Because he has never learned to accept inferiority, to fail courageously, he finds himself in unconscious and sometimes conscious terror of failure. To be at peace with himself he must excel. Already we see such a child—too ambitious for success—living before an audience which he must always please. The audience consists of himself and all the world besides, and before this audience he dare not fail.

Parents, moreover, often make the mistake of loading down their children with their own ambitions. Frustrated themselves, they come to feel an exaggerated satisfaction in their children's "successes." The child, in turn, sensing that much is expected of him, and afraid to disappoint both himself and his parents, whips himself still further toward his already crystallized though usually unconscious goal of superiority.

It is easy to understand that for such children life is a dangerous place. The attempt to achieve a goal of individual superiority necessitates a constant battle with other individuals, most of whom have an identical goal for themselves. Life becomes thus a continuous competition, with peace of heart dependent upon success. No wonder such a child labors under tension, too often ill-understood. This tension is further intensified if the child has grown to demand not only a sense of superiority as his goal in life, but absolute superiority, *i. e.*, perfection.

A child so trained faces a future where, to achieve peace of heart, he must maintain this sense of perfection, and a sense of perfection is a very fragile thing. His constant fear is lest he see himself or be seen by others inadequate, imperfect. As he grows older and avoidance of mistakes becomes increasingly difficult, the child begins to restrict his world to those who look upon him with special consideration. He plays with himself rather than with others, prefers to stay with mother or father of whose good opinion he is certain, rather than risk the often unfavorable opinion of boys or girls of his own age. Such youngsters often grow up without the training for marriage which should result from the normal attractions toward the opposite sex of childhood and early youth. Self conscious and shy, with feelings of inadequacy becoming constantly more insistent, the boy or girl approaches unprepared the peril of matrimony.

For marriage is in fact a supreme danger for an individual so trained. Upon what stage is a perfect part more difficult to play

than upon the stage of matrimony? If a sense of perfection be essential, does not wisdom urge escape from marriage at any cost? The escape is sometimes partly conscious, sometimes wholly unconscious. Many reasons are discovered to make marriage inadvisable. A woman may idealize men to such a degree that no man will ever come up to her expectations; or a man may fall in love only with married women or with a woman already engaged. Toward girls with whom there are no obstacles against marriage, he feels no attraction. Again certain men or women retreat to safety by feeling no interest whatever in the opposite sex. Thus by devious means, the threat to self-esteem is circumvented. Such a man or woman may be totally unconscious of the mechanism at work, but marriage is effectively discarded.

Difficulties in the narrower sexual sphere often have a similar etiology. Sex feeling is inhibited by fear. Most men and women who believe themselves sexually inadequate (or prove to be so in marriage) are inadequate because of fear. The dread of discovering themselves and being discovered other than perfect as a lover interferes with the physiology of propagation and may completely inhibit it. When the universal sex drive is felt and the outlet for its expression blocked, the period of self-gratification or of homosexuality may be prolonged beyond the normal, and such an individual come to look upon himself as a pervert, this fear, in turn, often interfering with all normal sex adjustment.

An important factor retarding or preventing normal adjustments to life is the conflict resulting from parents' shame or fear in discussing the question of sex with their children. It is almost incredible that men and women, all of whom have been conceived and born in an identical manner are unable to tell their own children about conception and birth, but such is the case even today. The generations who associated sex feeling with shame and evil seem to have handed on their fears, like a disease, to the parents of the present. And although the modern parent is more conscious of his duty to educate his child along these lines, such education is undertaken too often with trepidation and hesitancy or with such deliberate boldness that the child receives an emotional shock as a result. It is not what parents tell their children in so many words, but the state of mind which accompanies what is told that is important. A child may not understand, or may forget the facts, but he never forgets the emotional tone of the telling. If parents are not themselves adjusted to the subject of sex, wise though their words may be, their own shame and fear will be inevitably sensed by the child as the primary association with sex. For years thereafter, and perhaps forever, any sex feeling may be regarded as something shameful. If the ideals be high and self-esteem held dearly, such children are doomed to conflict between their normal sex drive and the necessity to retain their self-esteem. Neurotic symptoms are

frequently the result, and again the adjustment to marriage is often seriously endangered. Many women and some men are frigid in the marriage relation because sex feeling from early childhood has been associated in their minds with shame and evil.

In presenting some such outline of the mechanisms of neurosis to each patient, the analyst might say the cart had been placed before the horse, but for practical purposes a scaffolding of hypothesis must first be raised and the details later applied.

To make the patient aware of the fear or the unconscious conflict responsible for his own difficulty is the important step. By asking him to recall his earliest memories, by investigating his relationship to the other members of his family, by inquiry into early sex education and experiences, this can usually now be accomplished. The patient may often be brought to realize that his situation is in fact a very natural one, perhaps the inevitable result of early experiences and the repressions which have followed in their wake. If it is found that the patient's unconscious goal has been to preserve at any cost a sense of superiority necessitated by a false goal in life, and if such a patient can be made to realize that peace of heart should depend upon his doing the best he can and not upon personal perfection, the neurosis, no longer necessary for the protection of self-esteem vanishes.

Summary. The ideal of medicine has ever been and (in spite of necessary and laudable specialization in various fields) remains today the treatment of the individual patient as a whole. It is as human beings that we must function in this world—as human beings, that we must work and love and play—not as brain dissociated from heart, nor yet as heart dissociated from body. It is overconcentration upon the importance of a single organ considered apart from its relation to the entire body—in overemphasis of a symptom as against the cause—or, indeed, even of the cause as against the symptom—that the weakness of modern medicine lies.

The last 25 years have seen the rise of the "science" of psychiatry. We observe the various schools at war with one another—the camp of Freud repudiating the tenets of Adler, the followers of Adler repudiating the tenets of Jung. At best the various schools are unable to agree upon that human impulse which is the fundamental cause of all neuroses. Is it not possible that no one "cause" is always so—but that each alienist is sometimes right—and sometimes wrong?

It seems to us that it is the place of the internist, of the physician who is specialist in no one field but doctor in many, at least to attempt to discern, combine and apply what is good in the conclusions of each school. True it is that life is too short and the time of both physicians and patients too fleeting for wise selection and application to be always adequately and unerringly made—but it is the privilege as well as the duty of every internist to see his patient

as a human being—to recognize the fact that a sick body is often the result of a sick mind, as a sick mind is frequently the companion of a sick body.

Can we blame the psychiatrists for quarrelling among themselves over their own individual perceptions of the truth, when we, who possess the daily opportunity of studying and treating mankind "whole," persist in seeing him only as an animal, and relegate to others—or completely ignore—that vast and mysterious region whereon the emotions, thoughts and volitions play their tremendous roles?

REVIEWS.

Clio Medica Vol. V. Physiology. By John F. Fulton, M.D., Sterling Professor of Physiology, Yale University. Pp. 141; illustrated. New York: Paul B. Hoeber, Inc., 1931. Price, $1.50.

This small volume supplies a very useful summary of the history of physiology. It groups the discussion according to several of the major subjects of physiologic study, and this assists the reader to obtain a clear picture. The earlier studies of the circulation of Fabricius, Sarpi, and Caesalpinus which later reached fruition in Harvey's work are well described and enable one to see the familiar picture of the gradual evolution of knowledge. Interesting sections are devoted to the rise of the teaching laboratories, and the development of the American school, It is somewhat disappointing to find the field of neurologic investigations mainly neglected, but presumably the author considered that he had dealt with this aspect sufficiently in his other books. An interesting bibliography of articles of an historical character is appended. H. B.

Arterial Hypertension. By Edward J. Stieglitz, M.S., M.D., Assistant Clinical Professor of Medicine, Rush Medical College, University of Chicago. Foreword by Rollin T. Woodyatt, M.D., Clinical Professor of Medicine, Rush Medical College, University of Chicago. Pp. 280; 21 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, $5.50.

The author gives some interesting and original views which may, as Dr. Woodyatt suggests in his Foreword, be entitled to serious study. This should, however, decidedly precede their acceptance. Briefly stated, the pathogenesis of hypertension is explained as follows: irritation of arteriolar musculature by various sorts of stimuli (concerning which the author holds an enviable certainty of knowledge); irritation which leads to spasticity and continuous increased muscle tone, resulting in muscular fatigue, consequent muscular hyperirritability and more spasticity (so that the hypertension may automatically persist even after original stimuli have

ceased to act!), with eventually muscular exhaustion and degeneration, replacement fibrosis and a terminal arteriolar sclerosis. He condemns the use of iodids in treatment, but claims excellent results from bismuth subnitrate. As regards renal function, he champions the theory of a secretory activity of tubular epithelium.

R. K.

THE PAPYRUS EBERS. Translated from the German Version by CYRIL P. BRYAN, M.B., B.CH., B.A.O., Demonstrator in Anatomy University College, London, With an Introduction by PROFESSOR G. ELLIOTT SMITH, M.D., D.SC., LITT.D., F.R.C.P., F.R.S., Professor of Anatomy, University College, London. Pp. 167; illustrated. London: Geoffrey Bles, 1930. Price, 10s. 6d.

A WELCOME companion to Breasted's recent sumptuous presentation of the Smith Papyrus (reviewed in these columns, 1931, **181**, 129) is this description and translation of abstracts from the "longest and most famous of the documents relating to the ancient practice of medicine." Dating from the same approximate age as the Smith Papyrus, and like it presenting the records of an older folklore, these miscellaneous notes present an invaluable picture of the therapy of the ancient Egyptians with sidelights on their physiology, symptomatology and diagnosis. And yet, this book with translations from Joachim's German version, is the first of its kind in English. The author's pleasant, at times even breezy, style should help popularize an entrancing subject. A 35-page introduction by Elliott Smith gives some interesting firsthand illustrations of the problems of medical Egyptology and how they are often satisfactorily solved.

E. K.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY, VOL. VI. THE PATHOGENIC STREPTOCOCCI, MONOGRAPH XI. THE RÔLE OF THE STREPTOCOCCI IN SCARLET FEVER. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Hon. Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London, and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 470; illustrated. Baltimore: The Williams & Wilkins Co., 1930.

VOLUME VI of these Annals is devoted to the Rôle of the Streptococci in Scarlet Fever. The entire volume is given up to Monograph XI of this series of research studies. So rapidly has research work on Scarlet Fever been carried out, particularly during the last five years since the discovery of the Dick toxin, that about 1400 research papers are referred to in this volume. The information obtained is

enormous and quite varied. A very careful and profuse index is supplied, making this information quickly accessible.

About fifteen different proofs are offered showing that Scarlet Fever is caused by a specific hemolytic streptococcus which may be justly called the Streptococcus scarlatinæ. Attention is called to carbohydrate fermentation tests, the litmus test and the iodin test as dependable ways of differentiating various species of the hemolytic streptococci.

A most valuable aid to the research worker is presented in 13 full page illustrative plates which contain over 100 very exceptional photomicrographs. This volume, with volumes III, IV and V (published) and volume VII (to be published), represents an encyclopedia of information on the streptococci and the part they play in human and animal diseases. They cannot fail to be of great service to the future research worker in that they present the present state of human knowledge on the subject, and they will therefore form the basis of further researches for years to come.

W. K.

OUTLINES OF MODERN BIOLOGY. By CHARLES ROBERT PLUNKETT, Associate Professor of Biology, New York University. Pp. 711; 198 illustrations. New York: Henry Holt & Co., 1930. Price, $3.75.

THE outgrowth of photostated notes for a course in biology at Washington Square College, this book attempts the ambitious program of explaining as well as describing biologic phenomena on the concept of the living organism as a physicochemical mechanism. Protoplasm, nutrition, response, reproduction and evolution are discussed in necessarily elementary but admirably modern form, and without attaining simplicity at the price of superficiality. Three useful appendices offer a short classification of organisms, and of chemical compound symbols and nomenclature and a compact bibliography. It is the best of such textbooks that the Reviewer has had the fortune to meet and can be warmly recommended for medical as well as college scientific libraries. E. K.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE. VOL. II: COCCI, HEMOPHILIC BACTERIA. By Various Authors. Pp. 420. London: Medical Research Council, 1929. Price, £1.1.9 for this volume; for set, £8.14.9. Obtainable in the United States at British Library of Information, 5 East 45th Street, New York City.

FAVORABLE reviews of several volumes of the System of Bacteriology already have appeared in this JOURNAL. The present volume is

of similar character. Chapter I treats the staphylococci under the following headings: History, Morphology, Biochemical Reactions, Vitality, Distribution, Pathogenicity, Resistance, Classification and Treatment. Subsequent chapters are devoted to the Streptococci, the Pneumococcus, the Gonococcus, the Meningococcus, the Influenza Group of Bacteria, including Bacillus Influenzæ, Bacillus Koch-Weeks, Bacillus Hæmoglobinophilus Canis, Bacillus Parainfluenzæ and Bacterium Pneumosintes. Each of these chapters discusses at even greater length the morphologic, biologic and serologic characteristics of the various organisms. Special attention is paid to their pathogenic action and to methods of treatment.

The volume is more a discussion of the biologic and pathologic significance of the various organisms than a key for their identification and labelling with distinctive names. It furnishes a good exposition of the present-day knowledge of these organisms and their known or supposed relation to various diseases. An extensive bibliography appears after each chapter. The absence of an index is regrettable. G. R.

A System of Bacteriology in Relation to Medicine. By Various Authors. Vol. V. Glanders, Diphtheria, Tuberculosis, Leprosy, Brucella, Anthrax. Pp. 505. London: Medical Research Council, 1930. Obtainable in the United States at the British Library of Information, 5 East 45th St., New York. Price, £1/1/9; for the set £8/14/9.

Those who have been accustomed to struggle with numerous books in various languages in order to learn what is known of an important infectious disease, cannot but welcome a work to which he can turn in the full confidence that if he desire to inform himself concerning one of the subjects listed, he will find it adequately treated. The topics are presented from every important standpoint—historic, geographic, etiologic, morbid anatomic, histopathologic, micro-bacteriologic, micro-chemical, diagnostic, prognostic, immunologic, therapeutic, prophylactic and preventative.

It is true that the space allotted to each is necessarily limited, making it impossible for it to contain a complete review of the literature; but it does in each case give the facts omitting the theories and fancies popular in the past but better forgotten in the present. This is a rare virtue, for scientific literature is burdened with reiterated error and obsolescent theory appearing again and again in slavish conformity to the conception that no presentation can be satisfactory unless the entire antecedent literature be completely reviewed.

An American reader will scarcely escape the impression that his fellow countrymen have received less than their due share of recognition either in the text or in the references.

For example it seems to the Reviewer that Opie's work upon juvenile tuberculosis which seems to have been overlooked, deserved extended mention. It is also, perhaps, to be regretted that the volume contains no index of its own. J. McF.

THE SIGNIFICANCE OF THE PEKING MAN. By PROF. G. ELIOT SMITH, M.A., M.D., D.Sc., LITT.D., F.R.S. The Henderson Trust Lectures, No. XI. Pp. 20; 16 illustrations. Edinburgh: Oliver and Boyd, 1931. Price, Sixpence.

THIS lecture recently delivered at Edinburgh University by one of the most eminent authorities on human craniology tells the story of this most important discovery about primitive man in the author's usual clear and convincing manner. E. K.

THE PAPERS AND SPEECHES OF JOHN CHALMERS DACOSTA, M.D., LL.D., Samuel D. Gross Professor of Surgery at the Jefferson Medical College, Philadelphia. Pp. 440; 7 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, $6.50.

ONE of the most compelling, vivid and original and, if need be, caustic orators that medical Philadelphia has had the fortune to listen to in this generation has collected twenty-one of his papers and speeches for our edification. Dealing with the past and future of medicine, more than with the present, the book combines the wit of the *bonraconteur* with the vision of the prophet. As an instance of the former, he speaks of the Old Blockley Hospital, which was a striking example of the errors of municipal politics, "as reeling down the editorial pages of the newspapers." The Blockley politician believed in "Lucrum Gaudium"—the mosaic motto of the Pompeian house—"Gain is pure joy." He spoke of "snivel service reform." "He resembled a corkscrew in the fact that the more crooked he was, the more pull he had . . . he was apt to boast that whisky never gave him a head, which only goes to prove that whisky is not more powerful than the Almighty; . . . his parents were poor but Irish; he kept his party faith and everything else he could get his hands on" and so on through many lusty pages. In an essay on the surgeon he says: "A surgeon is like a postage stamp. He is useless when stuck on himself. A vain surgeon is like a milking stool; of no use except when sat upon. I don't see how any real surgeon can be vain. He is too often near to the inscrutable mystery of death—he sees too often the weaknesses of men—he too often stands at cross roads of judgment, knows that one way is the wrong way, but finds no sign to mark it—he too often

has to reproach himself for mistakes—he too often sees calamity tread on the heels of calamity—he too often laments, impotent to save, and watches 'Beauty and anguish walking hand and hand, the downward way to death.'"

Not only are home truths emphasized with the light rapier thrust, but artistic heights of description are reached (as in "Dickens' Doctors"); intimate biographies sketched (Larrey, Gross, Long, W. W. Keen, Pepys) and trenchant estimates made of the good and bad in our present medical tendencies. Truly a keen observer of men and deeds. E. K.

PRACTICAL RADIATION THERAPY. By IRA I. KAPLAN, B.S., M.D., Director, Division of Cancer, Department of Hospitals, New York City; with a special chapter on Applied *X*-ray Physics by CARL B. BRAESTRUP, B.Sc., P.E., Radiation Physicist, Division of Cancer, Department of Hospitals, New York City. Pp. 354; 225 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, $6.00.

THIS book offers a description of radiation therapy as practised at Bellevue Hospital. The book consists of 12 chapters. One hundred and twenty-nine pages are concerned with equipment and Roentgen ray physics, 16 pages on nursing care and organization and the remainder on the practical application of Roentgen and radium therapy and endothermy. The book is arranged very much like notes from which one would give didactic lectures; for instance, a picture of a case is shown on one page and on the opposite page the treatment employed is detailed. The book is presumably planned so that those who wish to begin Roentgen and radium therapy can refer to it and possibly obtain information as to the precise treatment employed in a given case. In many conditions the knowledge of the condition and the technique of practical radiation must be assumed, as the author discusses them very briefly. E. P.

PRACTICAL TREATISE ON DISEASES OF THE DIGESTIVE SYSTEM. Vols. I and II. By L. WINFIELD KOHN, M.D., F.A.C.P. Pp. 1125; 542 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $12.00.

IF the purpose of this text is to present the established knowledge of the gastrointestinal tract, it is well fulfilled by the author. The book is in general well written and thoroughly sound. It gives full information of the textbook type and displays practical good judgment in diagnosis and treatment. In the latter there are included a wide variety of measures discretely recommended and without the fads that too often mar writings on gastroenterology.

It is difficult to criticize adversely a book in which the essentials are well presented, but after this is said the Reviewer cannot see that it adds much to the subject. It seems to fail in this in general, although no individual section is especially deficient. One reason for this may be that the work represents an effort to integrate the entire gastrointestinal tract on the basis of normal and pathologic physiology. The numerous chapters on general considerations, of which that on physiology is very good, are the means of doing this, and they give a comprehensive idea of the factors underlying the behavior of the digestive system. This has resulted in a scattering and repetition of much of the information about a given topic with consequent incompleteness and confusion. In such a brief review it has not been possible to go into details, and it can only be stated that, although there is nothing to be condemned, the work lacks that keenness of selection and presentation which marks a great text. F. L.

BIOASSAYS—a HANDBOOK OF QUANTITATIVE PHARMACOLOGY. By JAMES C. MUNCH, Director of Pharmacologic Research, Sharp and Dohme; Pharmacologist, Bureau of Biologic Survey, United States Dept. of Agr. Pp. 958; 22 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, $10.00.

THIS is an exhaustive—and somewhat exhausting—compilation of the literature dealing with the methods of pharmacodynamics, their application to the quantitative testing of drugs (including vitamins) and the results obtained, the latter including 239 tables. Chemical methods are also presented in some cases (notably digitalis and ergot) but not in all. A brief chapter on the statistical interpretation of results is included. The author's primary purpose is stated to be the avoidance of unnecessary duplication of effort along these lines by making available under a single cover a record of what has already been done: the references cited total 6183. It is perhaps inevitable that even this impressive number is far from complete, not only with regard to the quantitative action of drugs, but also with regard to methods, but the book contains a tremendous amount of useful information. C. S.

PROTEUS, BAND I. VERHANDLUNGSBERICHTE DER RHEINISCHEN GESELLSCHAFT FÜR GESCHICHTE DER NATURWISSENSCHAFT, MEDIZIN UND TECHNIK, MIT FESTGABE FÜR WILHELM HABERLING. By PAUL DIERGART. Pp. 281. Bonn: Bonner Druck- und Verlagsanstalt, L. Neuendorff, 1931.

BEARING the same name as a similar periodical from the Rhine region, defunct for over a century, this interesting volume combines

the post-war *Proceedings* of the Rheinish Natural and Medical History Society with a Festschrift for Wilhelm Haberling on the occasion of his sixtieth birthday. It is not entirely clear whether it is an "occasional" volume or the first of another periodical on the History of Science. The excellence of its contents makes one hope for the latter. In addition to the special Fest articles, the volume contains lists of numbers and of programs and numerous abstracts of presentations. E. K.

QUANTITATIVE CLINICAL CHEMISTRY, VOL. I—INTERPRETATIONS. By JOHN P. PETERS, M.D., M.A., Professor of Internal Medicine, Yale University School of Medicine, and DONALD D. VAN SLYKE, PH.D., SC.D., Member of The Rockefeller Institute for Medical Research. Pp. 1264; 124 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, $12.00.

THE rapid growth of our knowledge of biochemistry in the present century and the successful application of much of it to the needs of clinical medicine has rendered an adequate presentation of the subject in book form increasingly desirable and increasingly difficult. The present volume is a successful treatment of the subject in a comprehensive manner—as might be predicted when the names of the authors are considered—and far removed in aim and scope from the ordinary handbook of clinical laboratory methods. Though the book was outlined 6 years ago along more conventional lines, it was fortunately recognized in time that normal physiological values and variations and an adequate discussion of the causes and mechanisms were necessary for an intelligent presentation. Not only did this prove so bulky that a second volume on methods was necessitated, but even this first reference book has devoted more space to the physiological sections than the clinical.

Of the 21 chapters, the lengthiest is that on acid-base balance (151 pages) with carbohydrate metabolism a close second (148 pages), and the chapter on hemoglobin third (135 pages). The chemistry of the proteins has been divided into 6 chapters which together total over 200 pages. The remaining third of the pages covers total metabolism; lipoids; organic acids and ketones; phenols; blood volume; and the chief bases and acid radicles. To attempt to evaluate all sections of such a comprehensive work would be impossible in a short review and often impertinent. One need have no hesitation, however, in recommending it as an authoritative and accurate statement. The references, too, at the end of each chapter are copious; for instance, there are 323 references to the chapter on hemoglobin, alone. They are of high grade, though disproportionately restricted in source.

The treatise illustrates in a sterling manner the application of biochemistry, physiologic as well as pathologic, to medicine. The

physician and the worker in the preclinical sciences will find it a well balanced and thoroughly modern discussion of the thousand and one chemical questions that today enter in the study of the normal or the diseased individual. The scope of the treatise may be gathered from citing the subheadings of one of the shorter chapters (on lipoids); nature, distribution and function of lipoids; fats; lipids; cholesterol; the metabolism of the lipoids; digestion, absorption and oxidation; the synthesis of lipoids; the excretion of lipoids; abnormal accumulation of lipoids in the body; the nature and concentration of the lipoids in blood; the blood lipoids in disease.

While the older fashioned clinician will doubtless be somewhat appalled at this presentation of one phase of what is now included in "Clinical Medicine," the book will be of immense value to those "internists" endeavoring to keep on the crest of the wave of the latest developments of scientific clinical medicine or to conduct investigations suitable for presentation at the most advanced clinical meetings. B. L. and E. K.

DISEASES OF CHILDREN. By BRUCE WILLIAMSON, M.D., Edin., M.C.R.P., Lond., Physician to the Royal Northern Hospital, London. Pp. 290; 50 illustrations. New York: William Wood & Co., 1931. Price, $3.50.

THIS is a limp leather, pocket-size manual for students. In condensing the subject of pediatrics into 290 pages, completeness has been sacrificed to brevity. Especially is this noticeable in the field of treatment, where specificity is not only desirable but essential to the beginner. From a diagnostic point, the book is more useful as the list of disorders is complete and the description of them clear. The author has arranged diseases according to their importance and frequency in general experience. This gives the book sound practical value, as subjects of purely academic interest are avoided. A feature which appeals to the reviewer is a short exposition of the normal prefacing each chapter. J. S.

SOME ASPECTS OF THE CANCER PROBLEM. Edited by W. BLAIR BELL, B.S., M.D. (LOND.), F.R.C.S. (ENG.), Hon. F.A.C.S., Fellow of King's College, London; Director of the Liverpool Medical Research Organization. Pp. 543; 273 illustrations. New York: William Wood & Co., 1930. Price, $20.00.

GRANTED that the nature and control of cancer is one of, or perhaps *the* greatest of medical problems of the day, any honest and sustained attack from an intelligent point of view must be attentively considered. It is, therefore, profitable that the well-known

work of the author during the past 20 years should be assembled and published in book form, even though the high price and the necessarily tentative quality of its conclusions may restrict its widespread private sale.

The resemblance of chorionic epithelium to carcinoma and the growth-inhibiting and abortifacient action of lead suggested to the author the use of lead in the treatment of cancer. The true cures obtained in some proven cases of carcinoma and the improvement noted in others seemed to justify as complete as possible a study of this working hypothesis. These 543 pages, many leading into distant physicochemical fields, are the present result and the end is not yet.

Lest the reader feel that he has been left in the air, a general summary is offered, including the elucidation (?) of evidence along four lines: histologic, physicochemical, physiologic and toxicologic. Careful perusal leaves at least one reader in the position deprecated; but perhaps that is, after all, the proper position at the moment in regard to this complicated subject. E. K.

TEXTBOOK OF HUMAN EMBRYOLOGY. By CLEVELAND SYLVESTER SIMKINS, Associate Professor of Anatomy, University of Tennessee Medical School, Memphis. Pp. 469; 263 illustrations. Philadelphia: F. A. Davis & Co., 1931. Price, $4.50.

THIS book considers the functional aspects of reproduction and of development, for the most part in the human, and is adapted for the use of medical students. The author has availed himself of the results of recent investigators, mostly of the last two decades. Where the illustrations are taken from original sources, as many of them are, the usual diagrammatic representations have been avoided. By assembling the information and illustrations in this manner the author has succeeded in presenting the contemporary viewpoint of the main facts of human embryology. A bibliography of 10 pages is included. W. A.

BOOKS RECEIVED.

NEW BOOKS.

Adventures in Biophysics. By A. V. HILL, Sc.D., LL.D., M.D., F.R.S., Foulerton Research Professor of the Royal Society. Pp. 162; illustrated. Philadelphia: University of Pennsylvania Press, 1931. Distributor: Charles C. Thomas, Springfield, Ill. Price, $3.00.

Progressive Medicine, Vol. II, June, 1931. Edited by HOBART AMORY HARE, M.D., LL.D., Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College. Assisted by LEIGHTON F.

APPLEMAN, M.D., Instructor in Therapeutics, Jefferson Medical College. Pp. 346; illustrated. Philadelphia: Lea & Febiger, 1931.

Eye, Ear, Nose and Throat for Nurses. By JAY G. ROBERTS, PH.G., M.D., F.A.C.S., Licentiate, American Board Otolaryngology. Pp. 213; 102 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, $2.25.

Textbook of Histology. By EUGENE C. PIETTE, M.D. Pp. 466; 277 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, $4.50.

Nosokomeion (Quarterly Hospital Review), No. 2, April, 1931. Pp. 434. Stuttgart: W. Kohlhammer. Price, R.M. 8.

Illustrations of the Methods of Reasoning. By DANIEL SOMMER ROBINSON, PH.D., Professor of Philosophy in Miami University. Pp. 346. New York: D. Appleton & Co., 1927. Price, $2.00.

Food Allergy. By ALBERT H. ROWE, M.S., M.D., Lecturer in Medicine in the University of California Medical School, San Francisco. Pp. 442. Philadelphia: Lea & Febiger, 1931. Price, $5.00.

The History of Medicine. By BERNARD DAWSON, M.D. (LOND.), F.R.C.S. (ENG.). Pp. 160; 31 illustrations. London: H. K. Lewis & Co., Ltd., 1931. Price, 7s 6d.

Health on the Farm and in the Village. By C. E. A. WINSLOW, DR.P.H., Professor of Public Health, Yale School of Medicine. Pp. 281; illustrated. New York: The Macmillan Company, 1931. Price, $1.00.

Guy's Hospital Reports, Vol. 81 (Vol. 2, Fourth Series), No. 2, April, 1931. Edited by ARTHUR F. HURST, M.D., Assisted by various contributors. Pp. 126; 1 illustration. London: The Lancet, Ltd. Price, 12/6 net.

Klinische Physiologie, Part 2. By PROF. DR. BERNARD STUBER, Oberarzt der Medizinschen Klinik der Universität Freiburg 1. Breisg. Pp. 142; 17 illustrations. München: J. F. Bergmann, 1927.

The Infant Welfare Movement in the Eighteenth Century. By ERNEST CAULFIELD, M.S., M.D. With a Foreword by GEORGE FREDERIC STILL, M.A., M.D. (CANTAB.), HON. LL.D. (EDIN.), F.R.C.P. (LOND.). Pp. 203; 8 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, $2.00.

A System of Bacteriology in Relation to Medicine. Vol. VIII. Fungi, Streptothriceæ, Normal Flora, Swine Erysipelas. By various authors. P. 389; illustrated. London: Medical Research Council, 1931. Price, £1.1.9 for this volume; for the set, £8.14.9. Obtainable in the United States at British Library of Information, 5 East 45th St., New York City.

NEW EDITIONS.

Resistance to Infectious Diseases. By HANS ZINSSER, M.D., Professor of Bacteriology and Immunity, Medical School, Harvard University. Pp. 651; illustrated. Fourth edition completely revised and reset. New York: The Macmillan Company, 1931. Price, $7.00.

Diabetes, Its Treatment by Insulin and Diet. By ORLANDO H. PETTY, A.M., M.D., F.A.C.P., Professor of Diseases of Metabolism, Graduate School of Medicine, University of Pennsylvania. With an Introductory Foreword by JOHN B. DEAVER, M.D. Pp. 231; 13 illustrations. Philadelphia, F. A. Davis Company, 1931. Price, $2.00.

In this excellent book "the main object is the education of the diabetic in all matters pertaining to his health."

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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Some Lessons of the Distribution of Infectious Diseases in the Royal Navy.—In the third Milroy lecture, Captain S. F. DUDLEY (*Lancet*, 1931, **220**, 5613) brings out some interesting features concerning the epidemiology of undulant fever as a result of studies he has made on the old naval health reports of the British Navy. He notes that 100 years ago Malta was famous for its magnificant location, climate and freedom from disease; whereas 50 years later the British naval officer who was ordered to Malta went there with fear and trembling on account of the large number of cases of fever that occurred in that community. The fever rate had more than doubled from that of 50 years ago. In studying the influence of undulant fever on ships' crews, he notes that at this period the illness of the Mediterranean fleet as a result of febrile disorders had nearly trebled. It remained high until 1900, when the relationship between Brucella infection and goats led to the prohibition of the latters' milk in the Mediterranean fleet. Without discussing in detail this interesting lecture, Dudley points to several features which are of moment in his presentation. He thinks that after the undulant fever had been introduced into the ships as a result of the drinking of infected goats' milk, the infection may possibly have been transmitted directly from man to man. He holds that the disease evidently did not exist prior to 1860; otherwise it would not have escaped the notice of naval surgeons, and he substantiates this statement by referring to Theobald Smith's statement that the appearance of Br. abortus type of undulant fever prior to 1922 cannot be explained by the disease having escaped the notice of American physicians. More particularly is this point stressed in conjunction with the fact that since 1897 Br. abortus has been known to be present in cows' milk. It is suggested that the bovine type of brucella infection has increased its infectivity for man by passage through the pig or goat or that the present type of brucella infection may be derived from imported caprine strains. Some such condition must exist as in Porto Rico, where Br. abortus infection is extremely prevalent in cattle.

The strains isolated there are practically nonpathogenic to man. The author says that the recent types of brucella organism may be the development of passage through the host in which these organisms resided. It is quite possible that the present-day type of undulant fever may be due to the "attempt of an occasional parasite of man, which had wandered out of its specific host, the goat, to adapt itself to a purely human environment."

Experimental Acute Glomerulitis.—The reports of investigators attempting to produce glomerular nephritis in animals through the medium of injected bacteria with the products of their growth have been most contradictory, write LUKENS and LONGCOPE (*J. Exper. Med.*, 1931, **53**, 511). They therefore devised a series of experiments to find out if an induced state of hypersensitiveness could be produced through material which might, when brought into concentrated form through contact with the renal circulation, produce some altered response of the kidney cells. Without going into the details of the experimental methods, suffice it to say that injections of killed hemolytic streptococci were made into the left renal artery, the contralateral kidney being used for control, and the animals were sensitized. Fifty-two rabbits were used; 23 were sensitized and 29 normal. They were killed at various times after the intra-arterial injection. In view of the fact that particulate matter was found in the small bloodvessels of the injected kidney, it was necessary further to control the experiment by the injection of inorganic matter in the form of a bismuth salt. Experiments proved that an acute glomerulitis resembling very closely certain types of glomerular nephritis in man might be brought about through the injection of suspension of killed streptococci. The histologic lesion produced consisted of hyalin thrombi in the capillaries, often with focal distribution, but at times so diffuse that nearly every glomerulus was involved. Glomerular changes consisted chiefly of necrosis and exudation, but there was also injury to the tubular endothelium and the interstitial tissue. The study of the sections suggests that the retention of clumps of dead streptococci in the capillaries of the glomerulus is the cause of the pathologic changes, but it is not mechanical, as the picture was not reproduced when bismuth was injected. The suggestion, therefore, is advanced that the presence of these bacterial bodies in the glomeruli is of extreme importance, particularly when occurring in the sensitized rabbit whose glomeruli are acted upon by the disintegrated products of the dead streptococci.

SURGERY

UNDER THE CHARGE OF
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Extravasation from the Ureter.—GEISINGER (*Ann. Surg.*, 1931, **93**, 544) state that extravasation from the ureter in the absence of external traumatism is an unusual lesion of grave significance, herewith exhib-

ited in 3 cases. In all 3 instances the causative factor apparently was necrosis from impaction of a calculus within the ureter. The clinical picture depends upon the amount of extravasation, the virulence of the associated organism and the tissue reactions of the patient. Rapidly spreading infection may result or the process may become localized, with or without abscess formation. The fact that one of the cases recovered entirely without operative intervention on the affected side, is interesting and suggestive. As a rule, however, the condition will be frankly surgical. The time for the application of this surgery and the type of operative procedure undertaken, will be dictated by the conditions obtaining in the individual case.

Peptic Ulcer.—EMERGY and MONROE (*Am. J. Roent.*, 1931, **25**, 51) say that a study has been made of the value of the Roentgen ray to the clinician in following the treatment of patients with ulcer of the stomach or duodenum. The accuracy of the Roentgen examination is shown to be high as compared with most kinds of laboratory procedures. However, it is a mistake for clinicians to place implicit confidence in the results of the Roentgen findings and to discard entirely the older methods of investigation. It was found that a correct diagnosis was reached in 93 per cent of those patients having an ulcer. Retention as shown by Roentgen examination was found to give a true picture of clinical retention in 67 per cent of cases. The presence or absence of tenderness over an ulcer was found to have no clinical value. A study of the Roentgen findings and the clinical symptoms shows that it is not possible to diagnose a healed duodenal ulcer by the Roentgen ray. Moreover, the data support the idea that duodenal ulcer is a chronic disease which is rarely cured by treatment (medical).

Acute Intestinal Obstruction.—OCHSNER (*Surg., Gynec. and Obst.*, 1931, **52**, 702) says that in all cases of ileus there are varying degrees of vascular occlusion. The prognosis in ileus depends upon the length of time which has elapsed since the onset, the location of the obstruction and the previous therapy. Blood chemistry determinations are of value for prognosis and proper treatment. Symptoms and signs of ileus are usually characteristic. Plain roentgenograms of the abdomen with the patient in the upright position without the administration of contrast media are of value in diagnosing ileus. Early operation or relief of obstruction in ileus is imperative. Enterostomy is of value in both the adynamic and obstructive types of ileus, provided enterostomy alone is not employed. Splanchnic block, preferably by means of splanchnic analgesia (Koppis) is of distinct value in adynamic ileus. Drugs are of little, or no value, in the treatment of ileus.

Studies on High Intestinal Obstruction.—ARMOUR, BROWN, DUNLOP MITCHELL, SEARLES and STEWART (*Brit. J. Surg.*, 1931, **18**, 467) state that death in untreated cases of high intestinal obstruction is preceded by the progressive development of severe alkalosis, by gross lowering of the blood chlorid and at the last, by an increase in the blood urea. For some days before death, the urine is chlorid free and the stomach contents contain no free hydrochloric acid, though their total chlorid

content is normal. It is immaterial whether the bile and pancreatic juice enter the intestine above or below the obstruction. The time of survival is greater the lower the obstruction. Administration of both chlorid and water below the obstruction causes the chemistry of the blood, urine and stomach contents to remain normal and also greatly prolong life. Death ensues only after some four weeks and cannot be attributed directly to the obstruction. With peptone and carbohydrate added to the chlorid and water, life can be prolonged for seven weeks or more. Withdrawal of the chlorid then brings about death with the usual clinical and chemical symptoms. The occurrence of Bacillus welchii in the stomach contents is the same in treated and untreated animals. It is concluded that death is due not to toxemia, but to the clinical changes following the loss of chlorid and water and is prevented by their supply. Treatment therefore consists in supplying chlorid and water until continuity of the intestinal canal has been reëstablished. There is no evidence that excessive breakdown of tissue protein is an essential accompaniment of high intestinal obstruction.

THERAPEUTICS

UNDER THE CHARGE OF

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Paravertebral Alcohol Injections in Angina Pectoris.—This procedure has been employed extensively by PLETNEW (*Zeitschr. f. Kreislaufforsch.*, 1931, **23**, 177), who reports upon the duration of the results obtained. Pletnew believes this method to be far preferable to the various operative procedures upon the ganglia and vegetative nerves because it is generally equally effective and because the operative procedures are associated with 12 to 18 per cent of immediate mortality. To secure lasting results Pletnew finds it necessary to make systematic repeated injections of 5 cc. of a 1 per cent novocain solution in the region of each ganglion, followed a few minutes later by 5 cc. of 70 to 80 per cent of alcohol. Such injections should be repeated weekly. Before the injection the patient should be prepared by receiving a hypnotic on the preceding evening and a dose or morphin or pantopon 2 hours before the treatment. No ill effects have followed this procedure except in rare instances where the alcohol has apparently been injected directly into the ganglion, rather than into its immediate neighborhood. In such cases an immediate attack of anginal pain has been induced, but it has passed off promptly. In view of the latter occurrences Pletnew believes it possible that fatal accidents may occur

from such injections, but he has not seen any. By means of these repeated efforts chemically to cut the nerve connections between the heart and spinal cord he has obtained satisfactory lasting results in 3 of 22 cases; fairly lasting results in the majority of the remainder and has met with total failure in only 2 cases, in both of whom sympathetic nerve operations were subsequently necessary.

Rather Rare Toxic Manifestations of Tobacco.—The majority of the toxic effects of tobacco are acute and disappear promptly with cessation of the use of nicotine. LIPPMANN (*Klin. Wchnschr.*, 1931, **10**, 169) reports certain rather rare but more serious effects. The appearance of angina in a group of smokers is probably due to the vasoconstrictor effect of nicotine on the coronary arteries. Cases are reported in which repeated omission and resumption of smoking resulted in the disappearance and recurrence of the angina respectively. It is suggestive that in some cases nicotine may cause elevation of the blood pressure. Smoking is occasionally responsible for pain over the extremities. The vascular spasm responsible for the pain disappears often only after the complete exclusion of tobacco. Chronic intestinal symptoms, such as constipation and cramps are noted among rather young smokers.

Insulin-sensitive and Insulin-resistant Diabetes.—That certain complications of diabetes mellitus are associated with a decrease of the beneficial effect of insulin is well recognized. FALTA and BOLLER (*Klin. Wchnschr.*, 1931, **10**, 438) now call attention to the group of cases which exhibit insulin resistance regularly without the presence of complications. The pathology present in this group is varied. Most frequently there exist endocrine imbalance, liver disease, encephalitis and psychic disorders. The authors describe test methods which allow the estimation of the degree of resistance. In applying these one finds relative insulin resistance surprisingly often. Of a group of 74 patients, 52 showed some degree of insulin resistance. In general, resistance is more apt to be present among elderly individuals with obesity or arterial hypertension. The authors conclude that human diabetes mellitus cannot always be explained by an insufficient functioning of the islands of Langerhans.

PEDIATRICS

UNDER THE CHARGE OF

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Tuberculosis in Infants and Children.—HAMIL (*Am. J. Dis. Child.*, 1931, **41**, 1023) states that the supravital test gives a simple and accurate method for the laboratory study of the white cells in any disease. Monocytes are increased above the normal figure in active tuberculosis.

This observation is constant in severe tuberculosis, and the modified type of this cell predominates in severe and terminal stages of the disease. This type of monocyte is found in the blood of patients who do not have tuberculosis and is therefore not pathognomonic of the disease in infants and children. The lymphocyte is the only type of cell in the circulating blood which appears to have a constant relation to the tuberculous process. The total lymphocyte count is decreased below the normal figures in all active types of tuberculosis, this decrease depending on the severity of the disease. The lymphocyte count is increased in the healing stage, the constancy of this increase depending on the progression of healing. The total white blood cells and total neutrophils are increased in the terminal stage of severe tuberculosis. An increase in neutrophils is not constant in cases with ulceration and the formation of abscesses. The ratio of monocytes to lymphocytes is increased in active tuberculosis, this increase depending on the severity of the disease. It is due to both an increase in total monocytes and a decrease in lymphocytes, the latter factor being the more constant. As healing occurs, there is a decrease in the ratio, which is fluctuant until the healing is well advanced. In cases with multiple lesions in different pathologic stages, no reliance can be placed on the monocyte-lymphocyte ratio to determine the status of the tuberculosis. The tuberculin skin test and treatment with ultraviolet light, in cases of chronic and advanced healing tuberculosis, cause a change in the monocyte-lymphocyte ratio, and blood studies should be interpreted in the light of such influencing factors. He suggests that fluctuations in the different types of white blood cells in the peripheral circulation of patients with tuberculosis are due to stimulation of the reticular cells to proliferation by products of the tubercle bacilli and the tuberculous lesions rather than either to the simple presence of tubercle bacilli in the body or to the demand for the different types of cells according to the type or stage of the pathologic lesion. The great value of the white cell picture in tuberculosis in children lies in the distinction between active severe tuberculosis or an early healing tuberculosis and an advanced healing or latent tuberculosis in the child who shows some of the clinical signs of tuberculosis but no definite symptoms by which to determine the status of the pathologic process. Many children are brought to the practitioner for examination solely on the history of contact with tuberculous patients. They may show only a positive tuberculin test, which in children is a significant sign, and perhaps a positive D'Espine sign or a suggestion of hilar or suprahilar shadow beyond the normal limits. In such a case, the symptoms may be slight and in any event variable, although the pathologic process may be relatively extensive and rapidly progressive. A study of the white cells in such a case and a comparison of the total figures for each cell type with the normal total figures, and a computation of the monocyte-lymphocyte ratios will aid in determining whether the child should be permitted the freedom of the home life, or whether it should be subjected to further observation under tuberculosis management. There is no constant observation in the study of the white cells in the peripheral blood of children with tuberculosis that would warrant a diagnosis of tuberculosis without the support of clinical evidence. By the use

of supravital technique, an accurate and thorough study can be made of the different types of white blood cells. The study of the total number of monocytes and the total number of lymphocytes can be made by a fixed smear equally as well.

Premature Infants.—CRAWFORD (*Arch. Ped.*, 1931, **48**, 293) presents a study made of 231 prematures seen in 4495 deliveries, which was an incidence of 5.2 per cent. The average mother of 21 years had 2 months prenatal care and 91.8 were in good health. The cause of prematurity was determined in 91 cases as follows: syphilis, 31; twins, 26; toxemia, 12; placenta previa, 5; and other lesser causes. The average birth weight was 4 pounds, with a loss of 7 ounces for the first 5 days. The birth weight was usually regained by 11 days, and on discharge upon the twenty-first day the weight averaged 4 pounds and 14 ounces. Gavage feeding was necessary in 17.4 per cent. Temperature was maintained in all cases by using a closed bed heated with electric lamps. Death occurred in 82 cases or 35.5 per cent and was due to the following causes: prematurity, 50 per cent; syphilis, 23.2 per cent; pulmonary infection, atelectasis and intracranial hemorrhage each 5 per cent.

Interpretation of Pain in Infancy.—SHELDON (*Brit. Med. J.*, 1931, **1**, 530) says that the commonest effect of pain on a baby is to make him cry, and he feels that much help is to be gained from a study of the characters of this expression. Pain is by no means the only cause of a baby's crying. Hunger, cold, soiled napkins, or simply a desire to be amused may be contributing factors. It is not until the child exercises his will that crying due to temper makes its appearance so that this cause of crying is exceptional under 6 months of age. The features that should always be noted the cry is intermittent or continuous; whether it is a piteous wailing or a short, sharp scream; and whether it occurs at any particular time of the day or night. It is important to know the relation to the ingestion of food, and whether it is relieved or aggravated by the ingestion of food. Belching of gas often relieves the crying. It may be that the disturbance occurs only after sucking, after micturition or after defecation. Under the stress of severe pain the infant may not cry because of holding his breath, as so often seen in severe colic. The posture during the attacks of pain is important. The hips may be flexed so the thighs are on the abdomen, while the arms may be bent, with the elbows firmly pressed against the sides. In other cases the infant may be extended rigidly, with arched back, so that he supports himself on his head and heels. In many instances with careful clinical examination areas of distinct tenderness associated with pain may indicate the localization of the pain.

The Simplified Treatment of Empyema in Children.—NOEGGERATH (*Münch. Med. Wchnschr.*, 1931, **78**, 303) has returned to the older method of treating this condition because in resection of ribs the prognosis is rather unfavorable, and because pleural puncture, whether done only once or whether repeated, brings unsatisfactory results, especially in young children. He recommends an intercostal pleurotomy with the knife. Drainage is effected by means of a rubber drain.

Simple suction is done by a double bandage with plenty of bandage material which can be replaced easily. Besides its simplicity the method has three advantages. For the patient it is advantageous because the child bears this slight intervention much better than repeated punctures and is not inconvenienced by the tubes of the ordinary suction method. The nursing is simpler because the tubes are not long ones that might be bent or torn out. The physician values the method because it is simple and does not require any special instrument. In comparison with other methods the therapeutic results of the pleurotomy with subsequent drainage are favorable especially in young children less than 2 or 3 years of age.

DERMATOLOGY AND SYPHILIS

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Intradermal, Scratch, Indirect and Contact Tests in Dermatology.—Ramirez and Eller (*J. Am. Med. Assn.*, 1930, **95**, 1080), report the comparative study of four types of sensitization tests on a series of 500 patients with dermatoses in whom the etiology was suspected to be of allergic origin. They conclude that: (1) The patch or contact method is superior to other methods in determining susceptibility to external irritants, especially those of nonprotein structure; (2) the intradermal method of testing is more sensitive than the scratch method but it is more apt to produce false local reactions as well as severe systemic reactions in the highly sensitive. It would seem advisable to use the scratch method first and check up with the intradermal; (3) the indirect test, using the Prausnitz and Küstner method of local passive transfer, is particularly useful in young children who will not tolerate a large series of tests as well as in patients with persistent hyperirritability of the skin or where a dermatosis is so generalized that direct testing is impracticable.

Toilet Water Dermatitis.—Lane and Strauss (*J. Am. Med. Assn.*, 1930, **95**, 717). The authors direct attention to the possible injury to the skin from the denaturants such as diethylphthalate and quinin hydrochlorid used in the preparation of toilet waters. They describe in detail a peculiar dermatosis which has frequently been recognized by Continental observers since first described in 1916. This condition is known as berlock dermatitis and is due to the application of eau de

cologne containing oil of bergamot particularly after the rather long exposure to sunlight often associated with sea bathing or after excessive exercise with profuse perspiration. Clinically the dermatosis is seen most commonly on the neck, chest, back and shoulders, and consists of an inflammatory zone ranging from mild erythema to wheals or even vesiculation followed by a bizarre pigmentation in streak formation with the greatest intensity of pigmentation at the lowest portion of the irregular downward extensions. The name berlock dermatitis indeed is derived from the fancied resemblance of the eruption to the pendants of a necklace or watch chain. The authors in closing mention the experimental attempts that are being made to produce pigmentation of depigmented skin, such as vitiligo, by the combination of an alcoholic solution of oil of bergamot and ultraviolet irradiation.

GYNECOLOGY AND OBSTETRICS

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Irradiation of Uterine Cancer.—A study of 417 cases of uterine cancer which were treated at the State Institute for the Study of Malignant Disease at Buffalo between January, 1919, and June, 1925, has been presented by SCHREINER and KRESS (*Am. J. Roentgenol.*, 1931, **25**, 359). Using the Schmitz classification, which is now well known, they found that radium irradiation supplemented with roentgen irradiation gave the following results in the treatment of carcinoma of the cervix. Five-year cures were obtained in 65 per cent of group 1, 27.7 per cent of group 2, 13.2 per cent of group 3, 1.1 per cent of group 4 and 6.5 per cent of group 5. Combining groups 1 and 2, which were the operable cases, 20 out of 52, or 38.4 per cent, have been clinically well five years or more. Groups 1, 2 and 3 in which, at the time of admission, it was thought possible to effect a cure resulted in 37 out of 181, or 20.4 per cent, being clinically well five years or more. The primary mortality was less than 1 per cent including all cases. Twelve patients died in from one to four years from intercurrent disease, there being no evidence of recurrence of the cancer. They believe that no other treatment could possibly have given the palliative results which were obtained in many of the remainder of the cases. Fistulæ occurred 26 times in the far-advanced cases in which re-irradiation was deemed advisable and this should be borne in mind in the treatment of such cases. Two bladder fistulæ healed spontaneously. As a result of his extensive

observations on the lethal radiation dose for cancer cells and the technique of the combined radium and roentgen treatment of uterine cancer, SCHMITZ (*Am. J. Roentgenol.*, 1931, **25**, 364) concludes that about one-half of the highly anaplastic cases, that is, transitional round and basal cell and true adenocarcinomas and solid adenocarcinomas will probably succumb to a radiation tissue dose of 2.5 skin erythema doses if they extend within a radius of 6 cm. from the cervical canal. About 40 per cent of adult squamous-cell carcinomas, malignant adenomas and papillary and gelatinous adenocarcinomas may be killed by a radiation dose of 4 to 5 skin erythema doses if contained within a radius of 3 cm. from the axis of the uterus. The good end results of radiation treatment might be improved if it became technically possible and safe to increase the applied dose either locally or by distant irradiations. He states that many factors must be considered, such as the maximal tolerance of normal cells to radiation, the influence of obliterating endarteritis on the normal tissue, the resistance of the ureters to radiation, the formation of heavy scar tissue and coëxisting infections. Such research is tedious and requires a continual follow-up of the cases for many years, but Schmitz believes that the progress made along these lines augurs well for the future of radiation therapy.

Salpingostomy.—Following a few years of primary enthusiasm, it became the fashion in this country to decry salpingostomy for the restoration of the tubal lumen as a useless operation. No doubt this attitude has been due to the paucity of favorable results which followed the operation as done in the American clinics. In Central Europe, however, this subject continues to receive considerable attention and favorable results are reported in an encouraging number of cases. It is possible that there are some details of technique which are practised there which are not observed as we do the operation and, therefore, we shall briefly review the paper of MATWEJEWA (*Zentralbl. f. Gynec.*, 1931, **55**, 302), who believes that the operation has merit when properly performed on selected cases. In his technique the uterus and adnexa are first liberated from adhesions. If there is merely a simple closure of the tube, the fimbria are widely separated by a surgical forceps, the patulousness of the tube tested with a sound and the separated fimbria are sutured with three fine sutures in such a manner that the tubal mucosa is brought over the peritoneal aspect of the tube as much as possible and without injury to the delicate cells of the mucosa. If a hydrosalpinx is present, a healthy portion of the tube is selected and clamped and the tube separated ½ cm. medial to the clamp. Tincture of iodin is *not* applied in order to avoid any adhesive inflammation. The accompanying vessel is ligated and a new ostium is made on the healthy stump. He always adds a ventrosuspension of the uterus to the operation of salpingostomy and attributes much of his success to this point, since in this manner the tubes are held out of the pouch of Douglas and are not so apt to become entangled in new adhesions. In addition it is essential that tubal insufflation be performed periodically during the postoperative period in order to maintain the patulous condition of the lumen. The operation is absolutely contraindicated in the presence of acute inflammation.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Eye Observations in Epidemic Cerebrospinal Meningitis.—LEWIS (*South. Med. J.*, 1931, **2**, 101) reported 65 cases of meningococcic cerebrospinal meningitis examined during the course of an epidemic. He found eye changes in 49 per cent. In 13 of these, however, hyperemia of the disk and retina or engorgement of the retinal veins were the only abnormalities present. Definite lesions were observed in 29 per cent. Three cases developed paralytic convergent strabismus which persisted after recovery from the meningitis. The squint was found to have disappeared spontaneously in 2 of the patients who were reëxamined at a later date. Transient iridoplegia was noted in 2 cases and papillitis was present in 3 cases. In 1 case with internal hydrocephalus and 3 to 4 diopters swelling of the disk and retinal hemorrhages, autopsy showed a massive fibrinopurulent exudate covering the entire chiasm and the cerebellum. Two patients developed sudden total blindness, with dilated, stiff pupils but without any visible changes in the fundus. One patient died without regaining vision and the other gradually regained ability to count fingers in one eye and normal central vision in the other with greatly contracted fields; later he showed descending optic atrophy. The most frequent complication was acute iridochoroiditis or endophthalmitis, which occurred in twelve eyes of 9 patients. The main presenting symptom was loss of vision. Vitreous exudate was the main objective finding and only slight or moderate ciliary injection was present. Treatment, including intensive serum therapy, had no effect. Permanent blindness resulted in all the eyes involved. Two of the cases developed orbital cellulitis with marked proptosis and exposure of the cornea. In 1 of these cases ulceration of the cornea with perforation necessitated enucleation. Of the 32 cases with eye changes, 7 died, giving a mortality lower than the general death rate during the epidemic. Of the patients who recovered, 5 were permanently blind in one eye and 3 in both eyes; in the 7 of these patients the blindness was due to endophthalmitis.

The Clinical Significance of Retinal Arterial Changes and Retinitis in Cardiovascular Renal Disease.—GIPNER (*New York State J. Med.*, 1930, **30**, 961) calls attention to four types of sclerosis which may be differentiated in the retinal arteries: senile, secondary, primary and hypertension—and describes their points of difference. The component parts of the picture of retinitis in any type of cardiovascular renal disease are essentially the same, hemorrhages, cotton-wool patches,

serofibrinous exudation, edema-absorbing exudates and macular stars occur in both the hypertension and the nephritis groups. The differentiation of the retinitis of primary hypertension disease from that of primary nephritis depends mainly upon the recognition of the hypertension type of arteriosclerosis. Additional characteristics of the nephritis cases are anemia, more massive exudation, more complete macular stars and a greater tendency to retinal detachment. In certain cases of glomerulonephritis developing in the presence of previous hypertensive disease the associated retinitis will have features of both types. Within the hypertension group proper it is possible to distinguish three distinct grades of retinal changes which belong characteristically to three distinct types or grades of hypertension. Retinal arteriosclerosis, usually mild, without retinitis occurs in mild benign hypertension. When cotton-wool patches and hemorrhages are seen in addition to the arteriosclerosis the case should be considered to be of severe benign type. While these patients usually have a relatively high diastolic pressure with some damage to the heart, brain or kidneys, their prognosis is fair under proper management. The presence of well-defined edema of the disks in association with sclerosis, hemorrhages and exudates is characteristic of the retinitis of malignant hypertension. In these cases, as in the retinitis of chronic glomerulonephritis, the prognosis is poor. The average length of life is less than 2 years. Some patients with retinitis of malignant hypertension type die from cardiac or cerebral complications while renal function is still adequate. Others go on to terminal renal insufficiency. In patients with retinitis of nephritis terminal renal insufficiency is always present.

Chiasmal Syndrome Produced by Chronic Local Arachnoiditis.—Craig and Lillie (*Arch. Ophthal.*, 1931, **5**, 558) observed in 7 cases with syndromes suggesting tumor in the region of the chiasm, and in 1 case with a basofrontal syndrome that operation revealed chronic local arachnoiditis without adjacent or associated tumor. The diagnosis at operation was confirmed by necropsy in 3 cases. In the chiasmal group bitemporal hemianopsia for form and colors was present in 3 cases, bitemporal hemianopsia for colors in 1, homonymous hemianopsia for colors in 1 and partial homonymous hemianopsia with bilateral cecocentral scotomas in 1. The fundi were normal in 3 cases. The optic disks were pale in 2 cases and atrophic in 2. One case showed definite evidences of hypophyseal dysfunction. The sella turcica was normal in all cases. Improvement of vision occurred in 2 of the 4 patients who survived operation. In the case classified as a basofrontal syndrome examination revealed right nasal hemianopsia bilateral choked disks and a normal sella turcica. Fundus and fields returned to normal after operation. The authors feel that chronic local arachnoiditis affecting the optic chiasm is a definite clinical entity which cannot always be differentiated before operation from pituitary tumor, craniopharyngeal pouch cysts, glioma of the chiasm, aneurysm or suprasellar meningioma. Operation is justified in the inflammatory group even if the diagnosis is made prior to operation, since freeing the adhesions around the chiasm and optic nerves and allowing the encysted fluid to escape will often check the progress of the condition or alleviate the symptoms.

RADIOLOGY

UNDER THE CHARGE OF
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Conditions Commonly Called Colitis.—The word "colitis" has frequently been used to describe various types of intestinal dysfunction in which there is no demonstrable organic disease of the large intestine. BARGEN (*Am. J. Roent. and Rad. Therap.*, 1931, **25**, 308) protests against such misuse of the term. In cases of suspected intestinal disease painstaking and detailed anamnesis is of first importance. When discomfort or pain is present in the lower part of the abdomen the possibility of some disorder of the colon requires consideration. A regular routine of objective investigations is of great value in determining the presence or absence of disease. Roentgenologic studies have value in excluding from consideration intestinal neurosis which may be expressed in the conditions known as mucous colitis, spastic colitis and irritable colon. Colitis is an inflammatory disease of the colon and should not be diagnosed until thorough investigation has shown that inflammation, nothing less and nothing more, is present. Some other term, suggestive of part of a general bodily state, perhaps irritable colon, should designate the noninflammatory colonic disorders.

Uterine Hemorrhage Without Demonstrable Pathology.—Chronic uterine hemorrhage occurring in women without demonstrable pelvic disease is a common condition, according to MARTIN (*Am. J. Roent. and Rad. Therap.*, 1931, **25**, 349). Experimental evidence and operative material indicate that the etiologic factor is some abnormality of the endocrine system. An artificial menopause produced by radiation therapy, coupled with an anemia diet and iron medication, brings about excellent results in women over 40 years of age. In younger women a return to normal health is usually obtained through a combination of a small dose of intrauterine radium with Roentgen irradiation of the pituitary, an anemia diet, an iron tonic, an improved mode of living and the administration of glandular products.

Treatment of Tumors of the Bladder.—In the opinion of COLSTON (*Am. J. Roent. and Rad. Therap.*, 1931, **25**, 375) the presence or absence of infiltration is the most important factor to be determined before deciding on the treatment to be instituted. A careful cystoscopic examination is the most accurate method which we have at our disposal to determine this point. Noninfiltrating tumors are best treated by a combination of endovesical electrotherapy and direct radium application. By direct application of radium resistant tumors can usually be

made to respond promptly to the high-frequency spark and the chances of recurrence are markedly diminished. Infiltrating tumors should be treated by resection whenever this procedure can be safely carried out. When resection is impossible the tumor should be destroyed by diathermy through the open bladder and radium seeds implanted throughout its base. The intelligent treatment of bladder tumors can only be carried out by a combination of long experience with cystoscopic and electrotherapeutic methods, thorough knowledge of the technique of application and therapeutic results of radium and deep Roentgen therapy and thorough surgical experience in the treatment of these growths.

Urinary Tract Roentgenography by Means of Skiodan.—Urography after the administration of skiodan was successful in 7 out of 8 cases examined by OCHSNER and WISHARD (*Am. J. Roent. and Rad. Therap.*, 1931, **25**, 314), and the one failure was due to mechanical difficulties which prolonged the time of administration unduly. Tuberculosis, hydronephrosis and hypernephroma were among the lesions diagnosed. The writers agree with Beer, that the field for intravenous pyelography is much larger than the field for ordinary pyelography, but the former probably cannot completely supplant the latter.

The Postoperative Behavior of the Diaphragm.—Before and after a variety of abdominal operations, high and low, the behavior of the diaphragm was investigated by ALLEN (*Radiology*, 1931, **16**, 492). In 36 of the 94 cases studied the right diaphragm on the day after operation was sharply arched and high, and in 5 cases the left diaphragm was similarly affected, but in neither group was there roentgenologic or clinical evidence of disease in the corresponding lung. In some instances the affected dome was still high 3 weeks later, but a few subsided markedly after 3 or 4 days. The immediate cause of the condition is undetermined, but may be due to paralysis. In 57 per cent of the 94 cases both diaphragmatic arches were elevated, from causes which were more obvious and which apparently do not include paralysis. Both phenomena, but especially the unilateral high diaphragm, deserve attention, as the heart assumes a horizontal position suggesting displacement to one side or the other, and this, combined with a high position of one dome, may give an erroneous impression that atelectasis is present.

Endothelial Myeloma, or Ewing's Sarcoma.—Endothelial myeloma, or Ewing's sarcoma, while usually the most malignant of all types of bone tumor, is highly radiosensitive and very responsive to the toxins of erysipelas and Bacillus prodigiosus, according to COLEY (*Radiology*, 1931, **16**, 627). For this reason conservative treatment is justified for a limited period before resorting to amputation. Although many cases have been treated by radiation alone, or surgery and radiation, only one 5-year cure has been reported, and in this case no microscopic examination was made to verify the diagnosis. Treatment with the toxins of erysipelas and Bacillus prodigiosus, combined with radiation, preferably the radium pack, seems to be the best method of treating a primary operable case of endothelioma of the long bones. If the condition has

not shown improvement after 6 or 8 weeks, amputation followed by prolonged prophylactic toxin treatment should be considered. The author cites among inoperable cases 4 treated with toxins alone and 5 with toxins and radiation, all of which recovered and remained well for 5 years. Therefore, he thinks that few cases should be considered hopeless until such treatment has been tried.

Studies of the Effect of Roentgen-rays on the Healing of Wounds.—POHLE, RITCHIE and WRIGHT (*Radiology*, 1931, **16**, 445) exposed two groups of white rats to two qualities of Roentgen rays, preceding or following incisions in the skin. It was found that irradiation with either quality of the rays, in a dose of 1000 r at one sitting, from 1 to 30 days before the incision, did not affect the healing process perceptibly. Irradiation with a dose of 1000 r, with rays of either quality, immediately, 24 hours and 48 hours, respectively, after the incision, retarded the healing process, particularly in the 24-hour group, but did not interfere with the final formation of a smooth scar.

Skin Malignancy.—STEVENS (*Radiology*, 1931, **16**, 435) holds that local cures of cancer of the skin by modern expert radiation should approach closely to 100 per cent. The great importance of biopsy for diagnosis and the selection of treatment is emphasized. Biopsies, he thinks, are perhaps more safely performed with the radio knife than with the cold knife, especially when melanomas and moles are concerned. In general, he regards radiation and electric surgery as of greater value in the treatment of cutaneous malignant growths than surgery with the cold knife.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Acute Diseases of the Brain Due to Functional Disturbance of the Circulation.—DE VRIES (*Arch. Neurol. and Psychiat.*, 1931, **25**, 227) presents 4 cases in which the localized brain symptoms were due to elective softening of parts of the cortex and for which no organic vascular lesions could account. These cases are described in detail both clinically and pathologically. Case 1 was a toxemia of pregnancy, as evidenced by headache, premature delivery, icterus and convulsions. In addition, there was a mild chronic arteriosclerosis of the larger arteries at the base and of smaller intracortical arteries, together with chronic degeneration of ganglion cells. Foci of necrobiosis were found scattered indiscriminately in all of the layers of the cortex. These foci could not be explained by an organic change in the bloodvessels, and

it is not likely that a simple toxic action by the toxemia of pregnancy would cause such necrobiosis, because that theory would not explain the thromboses which were found in the foci nor the fatty degeneration of the vessel walls in other places. The author decides that: "One may, therefore, assume that the toxin acted on the arteries, causing a spasm which secondarily, through ischemia, caused macular necrosis of the nerve parenchyma and of the vessel walls themselves. The thrombosis probably occurred after the circulation had been restored; the hemorrhages in the necrotic parts occurred also after some circulation was present again." The patient in Case 2 had, in the fifth month of pregnancy, an attack of eclampsia or uremia. After Cesarean section the convulsive attacks stopped and the blood pressure came down to normal. Fever developed, however, and probably two days later paralyses were noted. At autopsy no organic vessel lesion was found to explain the softened laminated cortical areas in the brain, although there were thromboses of various pial vessels in other places. Fresh changes, due to septicemia, were apparent in many places—they were of the usual character: thromboses or small necroses with hemorrhage. Although the lesions found were due to cortical ischemia, the author finds it quite difficult to ascertain the cause. He remarks that: "It may be that the reverting of the blood pressure from its initial high value to the normal level played a more important rôle than had hitherto been believed." In Case 3 there was a fulminating encephalitis after hard exercise and exposure to the sun. On the fifth day of the disease there was a gradually progressing hemiplegia. From the first day increased intracranial pressure was present, and the coma had gradually increased. Cerebral edema or venous stasis, or both, might have been present, but these conditions do not cause necrosis of the gray matter unless aided by general anemia or vessel spasm. Here, as in Case 2, although there were areas of softening, which areas were laminated, there were found only normal vessel walls. The author here remarks that: "It is not now possible to give an explanation of the pathogenesis of the softening in this case. . . ." Case 4 had a severe gunshot wound, followed by severe shock. There was an infection of his wounds followed by septicemia, and death occurred 6 weeks later. Autopsy revealed hypertrophic meningitis, one encephalomalacic area in the left insula, and laminated softening of the gray matter around the panital operculum and in the depth of the interparietal sulcus. In his comments on this case the author states that: ". . . . no data are available to prove when the softening occurred, but probably this happened soon after the blood pressure fell to a very low level during the severe shock, which lasted for more than a day . . . sudden and prolonged intense fall of the blood pressure must have resulted in cerebral anemia with localized necrosis." The 4 cases described had two important points in common: (1) The softening was nearly exclusively localized in the gray matter, and in Cases 2, 3 and 4 took the form of laminated necrosis; (2) no organic change in the bloodvessels could be found to account for the necrosis.

Cerebral Birth Conditions With Special Reference to Cerebral Diplegia.—PATTEN (*Arch. Neurol. and Psychiat.*, 1931, **25**, 453) reports 46 cases of cerebral birth pathology. These cases he has divided into

two groups: (*a*) The first comprising those in which labor was considered in every respect normal; (*b*) those in which there was a definite history of difficult labor. The author defines a normal labor as "one which was not prolonged, in which the presentation was usual and no anesthetics or instruments were used and in which birth was not precipitated and the delivery could, in all respects, be considered spontaneous." The term "difficult labor," he states, is the exact opposite and includes Cesarean section. A composite summary of the two groups is given. Of his cases, 19 fall into the difficult labor group and 17 into the normal group. The sexes are about equally divided. The children of the difficult labor group never sat alone in 26 per cent of the cases and in the normal group in 25 per cent; never walked alone in 31 per cent of the difficult labor group as compared to 40 per cent in the normal group; 21 per cent of the difficult labor group never talked as compared with 29 per cent of the normal labor group. Frank evidence of motor disability was not observed in the majority of instances in both groups until sometime after birth. The usual history given was that these children were not considered abnormal until the time came when ordinarily they should be carrying out some of the motor functions of their age period. Not infrequently they were brought with the complaint that they did not sit up, could not walk or had never talked. The most interesting feature of the group, taken as a whole, was evidence of involvement of the pyramidal tract in a group in which labor was considered normal. The incidence of unilateral spasticity was greater in the difficult labor group, 21 per cent as compared with 11.1 per cent in the normal group. The remaining cases also offered a striking contrast, for the difficult labor group had 35.8 per cent, with no evidence of involvement of the pyramidal tract as compared to 11.1 per cent in the normal labor group. The occurrence of abnormal movement was not as great as one would expect. Nearly one-half of the total number showed such movements as the choreiform, athetoid and definite incoordinations in both groups, 47 per cent in the difficult labor and 48 per cent in the normal group. Convulsions were not as frequent as one might have expected: they occurred in 30 per cent of the difficult labor group as compared with about 10 per cent in the normal labor group. The estimation of intelligence in many cases was difficult. In the normal group intelligence was considered defective in all but 1 case; that is, in 96 per cent there was an estimated intelligence deficit. On the other hand, the difficult labor group had 6 cases in which the children were considered normal and 13, or 68 per cent, defective. The author remarks that from these data he believes it is possible to state that, irrespective of birth history, certain syndromes appear, showing practically identical symptoms. That "there is a disturbance of motor function more or less symmetrically distributed, giving evidence of disease or defect of the motor equipment of the individual and an accompanying low level of intelligence." He concludes that: "The frequent occurrence of bilateral motor involvement, together with defect in intelligence, indicates something more than the effects of trauma or vascular accidents in the neurologic conditions of the newborn infant. There exists probably a developmental defect or arrest which concerns either the integrity of the cortical cells or the proper myelinization of the corticospinal tracts and association fibers."

PATHOLOGY AND BACTERIOLOGY

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The Distribution of Lipoid in a Case of Niemann-Pick's Disease Associated With Amaurotic Family Idiocy.—Sobotka, Epstein and Lichtenstein (*Arch. Path.*, 1930, **10**, 677) reported a case of Niemann-Pick's disease occurring in a child, aged 10 months, who also presented evidences of amaurotic idiocy and who succumbed 8 months from the time that first symptoms were noted. Clinically the child presented enlargement of liver and of spleen, brownish pigmentation of skin and central red spots in the maculæ of both eyes. The total blood fat was 1430 mg.; blood cholesterol, 290 mg.; serum calcium, 12.2 mg.; serum phosphorus, 3 mg. Blood smears showed vacuolation of lymphocytes. At autopsy the liver weighed 180 gm. and all internal lymph nodes were enlarged and yellow. Sections showed large round or polygonal cells with diffuse vacuolization of their cytoplasm, throughout spleen, liver, lymph nodes, bone marrow, lung, kidney and intestine. These cells contained no neutral fat, contained some doubly refractive lipoids (cholesterol?) and large amounts of other lipoids. Sections of brain showed changes typical of those observed in amaurotic idiocy. The lipoid analyses showed an increase in lipoid phosphorus, in cholesterol to a lesser degree, and a depletion and disappearance of neutral fat from the organs of the body. This latter is a specific finding of Niemann-Pick's disease. The absence of kerasin serves to differentiate the condition from Gaucher's disease. This case tends to support the idea that Niemann-Pick's disease represents a widespread lipoid degeneration and that amaurotic idiocy represents the same degeneration limited to the central nervous system.

The Occurrence and Nature of Spontaneous Arteriosclerosis and Nephritis in the Rabbit.—Nusum, Elliot, Evans and Priest (*Arch. Path.*, 1930, **10**, 697) point out that in rabbits two types of so-called "spontaneous" arteriosclerosis occur. These are: (1) An elevated intimal lesion, and (2) medial degeneration, with calcification, and depression of the overlying intima. These two types of lesions occurred among 190 normal animals in the incidence of 3.1 per cent and 5.3 per cent respectively. In the same group of animals "spontaneous" nephritis occurred in 2.1 per cent. The nephritis was either focal in character, giving no clinical evidence of its presence, or was of a diffuse type giving rise to albuminuria and blood chemistry changes. In a group of 20 animals chosen because of evidence of spontaneous nephritis 10 were fed on a liver diet for 1 year. These animals showed somewhat

more extensive arterial lesions than noted in the animals fed upon a more representative diet. The liver diet appeared, also, to increase the degree of the renal damage, as evidenced clinically and pathologically. In regard to the etiology of these conditions, the high protein diet and infection are considered as possible factors.

The Transmissibility of Tick-bite Fever Virus to Guinea Pigs.—PIJPER and DAU (*Brit. J. Exp. Path.*, 1930, **11**, 287) have shown that the intraperitoneal injection of from 1 to 2 cc. of blood from patients suffering from tick-bite fever produced fever in guinea pigs. The normal rectal temperature of these animals was determined by them to be never greater than 102°. After the injection of blood the temperature rose 1° or 2° for several days. The temperature then dropped to normal, but was followed by a second rise which was more pronounced than the first one. Fever of similar nature was produced in a second group of animals by intraperitoneal injection of blood or brain pulp from the originally injected animals. In one instance the fifth animal passage was reached. Passages seemed to increase the virulence as judged by the temperature chart. Postmortem examination of these animals showed enlarged spleens, enlarged adrenals and markedly injected meninges. The authors concluded that South African tick-bite fever is caused by a living virus of the Rickettsia class.

Iron Storage in Splenectomized Rabbits.—FOWWEATHER and POLSON (*Brit. J. Exp. Path.*, 1930, **11**, 362) studied the storage of iron in the organs of rabbits to which colloidal iron was administered intravenously. One group of animals was splenectomized while the others were left intact. In these two groups each animal received 160 mg. of iron. A third group was kept as a control. Animals were killed in pairs at various time intervals up to 2 months and the lungs, livers, spleens and kidneys subjected to chemical and histologic examination. The outstanding feature of the results was the close similarity between the figures obtained for the first two groups of animals. The absence of the spleen did not materially affect the distribution of iron in the organs. The liver was the principal site of iron storage insofar as actual amounts were concerned. The concentration of iron in the spleen was much greater than in the liver, but the total amount stored there was minute in comparison. Histologic examination confirmed the results of chemical analysis. Pulmonary embolism of slight degree was constantly found, but active phagocytosis of iron thus held in the lung was in progress. The results did not yield any definite information on the transference of iron from the lungs to the liver. However, a transportation of iron from the lungs was suggested by the fact that in both series the lung iron content decreased steadily with passage of time.

Sclerosis of the Pulmonary Artery and Arterioles.—ROSENTHAL (*Arch. Path.*, 1930, **10**, 717) reports 3 cases of primary arteriosclerosis of the pulmonary artery, all of whom presented cough, dyspnea, cyanosis, edema and hypertrophy of the right ventricle of heart, thus being comparable to the syndrome described by Ayerza. The ages of the

patients varied from 43 to 48 years. On postmortem examination the lungs were dark gray, subcrepitant and moderately collapsed. Microscopically there was no peribronchial fibrosis or inflammatory reaction. The alveolar walls presented capillaries, some of which were dilated, some contracted, while many showed endothelial necroses. The main trunk of the pulmonary artery was slightly dilated. From the second order of vessels downward atheromatous changes became more marked. The earliest changes were a thickening of the media, due to muscle hypertrophy and elastic-tissue increase, and splitting of the internal elastic laminæ. Occasionally early hyalin and fatty changes in media and in intima accompanied the early thickening. As the regressive changes advanced the intima became thicker, fibrous-tissue proliferation occurred and the media, because of similar advancing changes, became thinned out. Thrombi became numerous. This process advanced to the point where the lumina of the vessels were obliterated either by organizing thrombus or by intimal proliferation. All 3 patients were in their occupations exposed to aspiration of gases or of particulate matter. These the author believes lead to chemical or mechanical irritation of the capillaries, with resultant spasm and even endothelial necrosis. This calls forth greater activity of the smaller arteries, with resultant muscle hypertrophy and elastic-tissue increase. With continued demands degenerative changes are established which give rise to the peculiar sequence of events described.

HYGIENE AND PUBLIC HEALTH

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The Types of Tubercle Bacilli Found in Tuberculous Lesions and in Nontuberculous Tissue in Man.—Aronson and Whitney (*J. Infect. Dis.*, 1930, **47**, 30) states that tubercle bacilli obtained from latent and progressive lesions and from nontuberculous tissue fall into two distinct groups with occasional atypical strains. The human type of tubercle bacillus is characterized by luxurious growth on glycerol agar and slight pathogenicity for the rabbit. The bovine type of tubercle bacillus is characterized by sparse growth in early generations on glycerol agar and high pathogenicity for the rabbit. The atypical strains may grow luxuriantly on glycerol agar and be highly pathogenic for the rabbit, or the cultures may grow sparsely and be slightly pathogenic for the rabbit. The glycerol reaction curve was not found to be specific for the respective types. No difference between the types

could be detected by means of the complement fixation reaction. From latent tuberculous lesions of human autopsy material there were isolated 83 cultures of the human type of tubercle bacillus, 3 cultures of the bovine type and 2 atypical strains. From progressive tuberculous lesions 96 cultures of the human type and 3 cultures of the bovine type were isolated. From lung tissue, pulmonary lymph nodes and mesenteric lymph nodes free from tuberculous lesions there were isolated 38 cultures of the human type and 2 atypical cultures. Three of the bovine cultures were obtained from guinea pigs inoculated with latent pulmonary tuberculous lesions from patients, aged 42, 65 and 65 years. Three cultures of bovine tubercle bacilli were obtained from the mesenteric nodes of children, aged 10 and 12 months, and from the lung of the second child. The atypical strains of tubercle bacilli were isolated from 2 patients, aged 57 and 70 years. Two of these cultures were obtained from nontuberculous lesions and 2 from a latent tuberculous lesion.

Recent Progress in Studies of Undulant Fever.—Hasseltine (*Public Health Reports*, 1930, **45**, 1660) studied the prevalence of undulant fever based on 442 cases which could be divided into three groups: (*a*) Those without significant exposure to livestock or carcasses (mostly urban cases); (*b*) rural cases having direct contact with livestock; (*c*) urban cases having direct contact with livestock or carcasses. These may be referred to as the milk, farm and meat groups. Group I, the milk group, had 198 cases (103 males, 95 females). Group II, the farm group, had 200 cases (191 males, 9 females). Group III, the meat group, had 44 cases (43 males, 1 female). The age distribution shows few cases below 10 years, and 67 per cent of cases occurred between 20 and 50 years of age. Every state in the Union furnished 1 or more cases. Bang's bacillus, the cause of contagious abortion in cattle, is considered the essential cause of undulant fever, as it prevails in the United States. Either of the varieties found in this country may infect man. Cattle may become infected with either goat or hog strains. Pasteurization of milk is regarded very effective in preventing the disease. This is borne out by the absence of the disease in cities having adequate pasteurization. Aside from cases due to milk, there is a large group of cases due to contact with infected animals or animal products, but there is no satisfactory means of dealing with this group of cases at the present time. Serologic tests in man and animals are regarded as aids in reaching diagnoses.

The Relation of Temperature and Humidity to the Course of a Bacillus Enteritidis Infection in White Mice.—Recent studies on the epidemiology of typhoid fever in Palestine have led to the conclusion that the seasonal epidemicity of intestinal infections could only be accounted for by the assumption that there is a seasonal variation in the resistance of the host to this type of infection. It was assumed that climatic factors, such as temperature, humidity, radiation, singly or in combination, effect disturbances in the physiologic equilibrium of the host which render him more or less susceptible to the invasion and localization of this group of microbes. In order to test this hypothesis

KLIGLER and OLITZKI (*Am. J. Hyg.*, 1931, **13**, 349) undertook a series of experiments on the effect of certain environmental factors on the course of an enteric infection. White mice from the same stock and of the same age infected with the same number of Bacillus enteritidis and kept at different temperatures and humidities reacted differently to the infecting microbes. At a low temperature and a high relative humidity (10° to 12° C. and 90) the infection is more severe than at higher temperatures (20° and 30° C.) and the same humidity. The fatality rate is the same but the incidence of liver abscesses is higher. At 30° C. the mice kept at a relative humidity of 90 are more severely affected than those kept at a relative humidity of 35°. Under the latter conditions the development of the infection is more rapid, but it is mild or inapparent in character, clears up rapidly and leads to relatively few deaths in comparison with the group kept at a high relative humidity. At 20° C. a higher humidity seems more favorable than a lower one; but the differences are not marked. It appears that the critical factor is not temperature alone nor humidity alone, but the combination of the two; probably the so-called "effective temperature." The authors state that these results are only suggestive and that much more work is required to clear up this problem. They are, however, significant and support the assumption of a seasonal variation in host resistance due to environmental influences. The method employed opens the possibility of a systematic study of the problem, and the investigations are being continued.

Heliotherapy and the Peripheral Blood.—HOEFFEL and LYONS (*Am. J. Dis. Child.*, 1930, **40**, 484) state that there is no justification for the belief that light rays, considered either collectively as including the entire spectrum or individually as ultraviolet rays, have any specific effect on the blood. The effect of light on the healing of a pathologic process, such as tuberculosis, cannot be distinguished from that exerted by other factors, the beneficial influences of which are well recognized.

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